

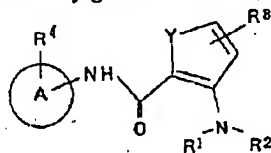
(57) (Abstract) (Amended)

Object

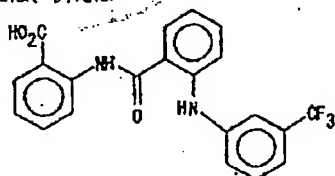
To put forward a novel aromatic amide derivative as ACC activity inhibiting agent effective in therapy of visceral fat syndrome which comprises a risk factor of adult diseases such as cardiac infarction, cerebral infarction, diabetes mellitus or the like.

Method of Solution

An aromatic amide derivative represented by general formula,



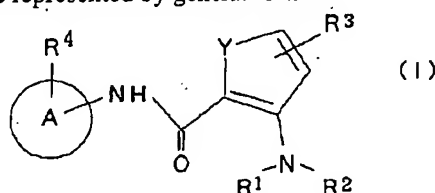
in an embodiment, represented by for example



Patent Claims

Claim 1.

An aromatic amide derivative represented by general formula



(wherein, R1 and R2 denote hydrogen atom, substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group. Furthermore, these R1 and R2 are not hydrogen atoms simultaneously, and moreover can form a 5-7 membered ring structure by bonding with nitrogen atom to which they are bonded and forming one body,

R3 denotes hydrogen atom, substituted amino group, substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted alkenyl group of C2-C12, substituted or unsubstituted alkynyl group of C2-C12, substituted or unsubstituted alkoxy group of C1-C12, substituted or unsubstituted

aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group. Y denotes groups represented by -CH=CH-, -N=CH-, -CH=N-, sulphur atom or oxygen atom, R4 denotes acid functional group and ring A denotes substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted cyclic alkyl group).

Claim 2

An aromatic amide derivative in accordance with Claim 1, wherein the ring A is an aromatic hydrocarbon group having substitution at 1, 2 position, heteroaromatic ring group having substitution at 1, 2 position or cyclic alkyl group having substitution at 1, 1 position.

Claim 3

An aromatic amide derivative in accordance with Claim 2, wherein R3 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, C2-C4 alkenyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, C2-C4 alkynyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group or C1-C4 alkoxy group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, and R1 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent.

Claim 4

An aromatic amide derivative in accordance with Claim 2, wherein R3 is unsubstituted C5-C12 alkyl group, unsubstituted C5-C12 alkenyl group, unsubstituted C5-C12 alkynyl group or unsubstituted C5-C12 alkoxy group, and R1 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent.

Claim 5

An aromatic amide derivative in accordance with Claim 2, wherein R3 is hydrogen atom and R1 is substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted alkyl group of C4-C12.

Claim 6

An aromatic amide derivative in accordance with Claim 1, wherein acid functional group is carboxyl group.

Claim 7

An aromatic amide derivative in accordance with Claim 1, wherein acid functional group is a group represented by general formula $R5CONHSO_2-$ (wherein, R5 is substituted or unsubstituted alkyl group of C1-C12, aromatic hydrocarbon group, substituted amino group or substituted or unsubstituted alkoxy group of C1-C12).

Claim 8

A drug comprising an aromatic amide derivative in accordance with any of Claims 1-7 or a pharmacologically acceptable salt thereof as an effective ingredient.

Detailed Description of the Invention

(0001)

Technical Sphere of this Invention

This invention relates to an aromatic amide derivative, in detail, a novel aromatic amide derivative having Acetyl-CoA Carboxylase (hereinafter it may be abbreviated to ACC) inhibiting activity.

(0002)

Technology of the Prior Art

Recently, it became clear that excess accumulation of neutral fat, in particular, triglyceride in visceral adipose tissue is the main risk factor of various diseases such as hyperlipidemia, hypertension, arteriosclerosis, cardiac infarction, glucose tolerance aberration or the like. In other words, fatty acid synthesis is activated in visceral adipose tissue, and it is considered that if this fatty acid is discharged to portal vein, it accelerates insulin resistance and furthermore it is taken into liver, used as raw material of triglyceride and discharged in plasma, and hypertriglyceridemia is caused.

(0003)

On the other hand, ACC is an enzyme that catalyses synthesis of Malonyl-CoA from Acetyl-CoA and is the rate-limiting enzyme in biosynthesis of long chain fatty acid. Moreover, it is known that Malonyl-CoA itself synthesised from Acetyl-CoA by ACC regulates the Carnitine acyltransferase that participates in the consumption of free long chain fatty acid as energy source. Moreover, it is thought that activation of ACC participates in activation of fatty acid synthesis in visceral adipose tissue. Accordingly, a drug that hinders ACC activity hinders biosynthesis of long chain fatty acid in vivo and at the same time promotes metabolism, thereby the quantity of long chain fatty acid is decreased in vivo, as a result biosynthesis of triglyceride is inhibited, and it has possibility as prevention and treatment drug of various diseases based on accumulation of visceral fat.

(0004)

Problems to be Overcome by this Invention

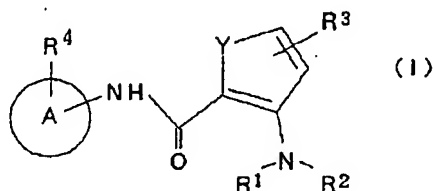
From such point of view, these inventors carried out assiduous investigations with an object to search ACC activity inhibiting agent effective in therapy of visceral fat syndrome comprising a risk factor of adult diseases such as cardiac infarction, cerebral infarction, diabetes mellitus or the like, as a result, newly discovered that excellent ACC inhibiting action was observed in aromatic amide derivative represented by following general formula (I), and completed this invention. Accordingly, this invention has an object of putting forward a novel aromatic amide derivative and salts thereof, moreover putting forward a drug containing these compounds as active ingredient, in particular the ACC activity inhibiting agent.

(0005)

Means to Overcome these Problems

In order to solve such object, this invention puts forward an aromatic amide derivative represented by general formula,

(0006)



(0007)

(wherein, R1 and R2 denote hydrogen atom, substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted

heteroaromatic ring group. Furthermore, this R1 and R2 are not hydrogen atom simultaneously, and moreover they can form 5-7 membered ring structure by bonding with nitrogen atom which they are bonded and forming one body, R3 denotes hydrogen atom, substituted amino group, substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted alkenyl group of C2-C12, substituted or unsubstituted alkynyl group of C2-C12, substituted or unsubstituted alkoxy group of C1-C12, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group. Y denotes groups represented by -CH=CH-, -N=CH-, -CH=N-, sulphur atom or oxygen atom, R4 denotes acid functional group and ring A denotes substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted cyclic alkyl group).

(0008)

Conditions for carrying out this invention

The aromatic amide derivative represented by aforesaid general formula (I) putting forward by this invention is a novel compound which has previously been unknown, and it has not been known that these compounds have ACC activity inhibiting action at all. However as it is made clear from results of later-described Pharmacological Test, it was revealed that these compounds had excellent ACC activity inhibiting action. Accordingly these compounds are extremely useful as ACC activity inhibiting agent effective in therapy in particular of visceral fat syndrome comprising a risk factor of geriatric diseases such as cardiac infarction, cerebral infarction, diabetes mellitus or the like. Moreover as other embodiments thereof, this invention is to put forward a drug containing aromatic amide derivatives represented by the aforesaid general formula (I) or salts thereof as effective ingredient.

(0009)

Below the aromatic amide derivative putting forward by this invention will be described in greater detail. In this specification, as "alkyl group of C1-C12", it may be straight form, branched form or cyclic form, and methyl, ethyl, n-propyl, 1-methylethyl, cyclopropyl, n-butyl, 2-methylpropyl, 1-methylpropyl, 1,1-dimethylethyl, cyclobutyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, cyclopentyl, 2,2-dimethylpropyl, n-hexyl, 1-methyl pentyl, 2-methyl pentyl, 4-methyl pentyl, 1-ethyl butyl, 2-ethyl butyl, 3,3-dimethylbutyl, cyclohexyl, n-heptyl, 5-methyl hexyl, 4,4-dimethyl pentyl, cycloheptyl, 1-methyl hexyl, 2-methyl hexyl, 1-propyl butyl, 2-ethyl pentyl, cyclohexylmethyl, 1,1-diethyl propyl, n-octyl, 6-methylheptyl, cyclo octyl, 1-methylheptyl, 1-ethylhexyl, 5,5-dimethylhexyl, 2-cyclohexyl ethyl, n-nonyl, 1-methyl octyl, 7-methyl octyl, 6,6-dimethyl heptyl, n-decyl, 1-methyl nonyl, 8-methyl nonyl, 7,7-dimethyl octyl, n-undecyl, 1-methyl decyl, 9-methyl

decyl, 8,8-dimethyl nonyl, n-dodecyl, 1-methyl undecyl, 10-methyl undecyl, 5-methyl undecyl, 9,9-dimethyl decyl and the like can be exemplified, and furthermore, these alkyl group may be substituted by various kinds of substituents. As such substituent, halogen atom such as chlorine, bromine, iodine, fluorine or the like, aromatic hydrocarbon group such as nitro group, amino group, cyano group, hydroxy group, alkoxy group, thiol group, phenyl, naphthyl and the like, heteroaromatic ring group such as thienyl, furyl, pyridyl and the like can be exemplified. Moreover, these aromatic hydrocarbon groups and heteroaromatic ring group may further contain substituent such as the said halogen atom, alkyl group, alkoxy group, nitro group, amino group, cyano group, hydroxy group, thiol group and the like.

(0010)

Moreover, "substituted or unsubstituted aromatic hydrocarbon group" is monocyclic or polycyclic, and furthermore it denotes aromatic hydrocarbon group which may contain one or more various kinds of substituents on the ring, and for example phenyl, methylphenyl, dimethyl phenyl, methoxyphenyl, dimethoxyphenyl, nitrophenyl, dinitrophenyl, chlorophenyl, dichlorophenyl, bromo phenyl, dibromo phenyl, iodophenyl, fluorophenyl, trifluoromethylphenyl, aminophenyl, hydroxyphenyl, mercaptophenyl, cyanophenyl, alpha-naphthyl, beta-naphthyl group are nominated.

(0011)

The "substituted or unsubstituted heteroaromatic ring radical" is a group of 5 or 6 membered ring containing at least one of heteroatoms such as nitrogen atom, sulphur atom, oxygen atom or the like as ring constituting atoms, and these may be condensed with benzene ring and furthermore may contain one or more various kinds of substituents on ring, and for example pyridyl, furyl, thienyl, indolyl, quinolyl, isoquinolyl, benzofuranyl, benzothienyl, imidazolyl, benzimidazolyl, thiazolyl, oxazolyl, pyrazolyl, pyrimidyl, pyrazyl, isoxazolyl, iso indolyl, pyrrolyl and the like are nominated.

(0012)

The "alkenyl group of C2-C12" may be branched chain or straight chain, and it is possibly exemplified by 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, ethenyl, 1-methyl ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 2-pentenyl, 1-pentenyl, 1,3-butane dienyl, 3-methyl butenyl, 1-hexenyl, 2-hexenyl, 3,3-dimethyl-1-butenyl, 4,4-dimethyl-1-pentenyl, 1,3-pentadienyl, 1,3-hexadienyl, heptenyl, octenyl, 2-cyclohexyl ethenyl nonenyl, decenyl, undecenyl, dodecenyl and the like, and furthermore, these alkenyl group may be substituted by various kinds of substituents. As the substituents, the same groups as substituents exemplified in aforesaid alkyl group of C1-C12 can be nominated.

(0013)

The "alkynyl group of C2-C12" may be branched chain or straight chain, and 1-propynyl, 2-propynyl, 1-methyl-2-propynyl, 1-ethyl-2-propynyl, ethynyl, 1-butylnyl, 2-butylnyl, 1,3-butadiynyl, 1-pentylnyl, 2-pentylnyl, 1,3-pentadiynyl, 1-hexynyl, 2-hexynyl, 1,3-hexadiynyl, 3,3-dimethyl-1-butylnyl, heptylnyl, octylnyl, cyclohexyl ethynyl, nonynyl, decynyl, undecynyl, dodecynyl and the like are nominated, and furthermore, these groups may be substituted by various kinds of substituents. As the substituents, the same groups as substituents exemplified in aforesaid alkyl group of C1-C12 can be nominated.

(0014)

Moreover, "alkoxy group of C1-C12" denotes the alkyl-substituted oxy group in which alkyl group has aforesaid meaning, and embodiment examples include methoxy, ethoxy, n-propoxy, 1-methyl ethoxy, n-butoxy, 2-methyl propoxy, 1-methyl propoxy, 2-methyl-2-propoxy, 1,1-dimethyl ethoxy, n-pentyloxy, 3-methyl butoxy, 1-ethyl propoxy, n-hexyloxy, 3,3-dimethyl butoxy, heptyl oxy, 4-methyl pentyloxy, cyclohexyl methoxy, octyloxy, nonyl oxy, decyloxy, undecyl oxy, dodecyl oxy and the like. Moreover, these alkyl group may be further substituted by various kinds of substituents. As the substituents, the same groups as substituents exemplified in aforesaid alkyl group of C1-C12 can be nominated.

(0015)

Moreover, "acid functional group" denotes hydroxy group, mercapto group, hydroxamic acid group, carboxyl group, phosphono group, sulfo group, sulphino group, sulpheno group, thio carboxyl group or amide, N-substituted amide and N-acylamido thereof. As N-acylamido group, for example groups represented by general formula $R_5CONHSO_2$ - (wherein, R_5 is substituted or unsubstituted alkyl group of C1-C12, aromatic hydrocarbon group, substituted amino group or substituted or unsubstituted alkoxy group of C1-C12) are nominated. As substituted amino group of R_5 , amino group wherein aforesaid substituted or unsubstituted alkyl group of C1-C12, substituted or unsubstituted alkenyl group of C2-C12, substituted or unsubstituted alkynyl group of C2-C12, substituted or unsubstituted alkoxy group of C1-C12, substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group are substituted onto nitrogen atom with one or two substituents, and furthermore, the substituents may bond together with nitrogen atom to which they are bonded and form 5-7 membered saturated heterocycle structure including heteroatoms such as 1-pyrrolidinyl group, piperidino group, 1-piperazinyl group, morpholino group, thio morpholino group, 1-perhydroazepinyl group and the like can be nominated.

(0016)

As acid functional groups, examples include carboxamido, phosphonamide, sulfonamide, sulfine amide, sulphenamide, thiocarboxamide, N-benzoyl carboxamido, N-phenyl carboxamido, N-benzoyl sulfonamide, N-(3-benzyloxy benzoyl) sulfonamide, N-(4-trifluoromethyl benzoyl) sulfonamide, N-benzyl sulfonamide, N-phenyl sulfonamide, N-(4-nitrobenzoyl) sulfonamide, N-benzoyl phosphonamide, N-benzoyl sulfine amide, N-benzoyl thiocarboxy amide, N-acetyl sulfonamide, N-propanoyl sulfonamide, N-(2-methyl) propanoyl sulfonamide, N-butanoyl sulfonamide, N-hexanoyl sulfonamide, N-decanoyl sulfonamide, N-dodecanoyl sulfonamide, N-(2,2-dimethyl) propanoyl sulfonamide, N-(2-cyclohexyl) acetyl sulfonamide, N-phenyloxy carbonyl sulfonamide, N-benzyloxycarbonyl sulfonamide, N-methoxycarbonyl sulfonamide, N-ethoxycarbonyl sulfonamide, N-butoxycarbonyl sulfonamide, N-hexyloxy carbonyl sulfonamide, N-(2-methyl) propoxy carbonyl sulfonamide, N-(2,2-dimethyl) propoxy carbonyl sulfonamide, N-octyloxy carbonyl sulfonamide, N-decyloxy carbonyl sulfonamide, N-dodecyl oxycarbonyl sulfonamide, N-phenylamino carbonyl sulfonamide, N-benzylamino carbonyl sulfonamide, N-methylamino carbonyl sulfonamide, N-ethylamino carbonyl sulfonamide, N-butylamino carbonyl sulfonamide, N-(1-methyl) ethylamino carbonyl sulfonamide, N-(2-methyl) propylamino carbonyl sulfonamide, N-(2,2-dimethyl) propylamino carbonyl sulfonamide, N-hexyl aminocarbonyl sulfonamide, N-cyclohexyl aminocarbonyl sulfonamide, N-octyl aminocarbonyl sulfonamide, N-decyl aminocarbonyl sulfonamide, N-dodecyl aminocarbonyl sulfonamide, N-(1-piperidinyl carbonyl) sulfonamide, N-(1-piperazinyl carbonyl) sulfonamide, N-(4-morpholyl carbonyl) sulfonamide and the like.

(0017)

In aromatic amide derivative represented by the aforesaid general formula (I), substituents R1 and R2 may bond together with nitrogen atom to which they are bonded and form aforesaid 5-7 membered saturated heterocycle structure.

(0018)

In aromatic amide derivative represented by the aforesaid general formula (I) put forward by this invention, ring represented by A is aforesaid aromatic hydrocarbon group or heteroaromatic ring group. As the substituted manner of these groups, it is preferred that acid functional group represented by R4 and groups having amide side chain are substituted at 1,2 positions, and moreover when A is cyclic alkyl group, the acid functional group represented by R4 and groups having amide side chain are substituted at 1,1 position.

(0019)

Moreover, in aromatic amide derivative represented by the aforesaid general formula (I), when R3 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, C2-C4 alkenyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, C2-C4 alkynyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent or C1-C4 alkoxy group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent, it is preferred that R1 is C1-C4 alkyl group containing substituted or unsubstituted aromatic hydrocarbon group or substituted or unsubstituted heteroaromatic ring group as substituent.

(0020)

Moreover, when R3 is unsubstituted C5-C12 alkyl group, unsubstituted C5-C12 alkenyl group, unsubstituted C5-C12 alkynyl group or unsubstituted C5-C12 alkoxy group, it is preferred that R1 is C1-C4 alkyl group containing substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted aromatic hydrocarbon group as substituent. Furthermore when R3 is hydrogen atom, R1 is preferably substituted or unsubstituted aromatic hydrocarbon group, substituted or unsubstituted heteroaromatic ring group or substituted or unsubstituted alkyl group of C4-C12. Moreover, it is preferred that acid functional group is group denoted by carboxyl group or general formula $R_5CONHSO_2-$.

(0021)

As aromatic amide derivative of this invention, for example following compounds are illustrated. 2-(2-(2-pyridyl) amino benzamide) benzoic acid, 2-(2-(2-thienyl) amino benzamide) benzoic acid, 2-(2-(2-furfuryl) amino benzamide) benzoic acid, 2-(2-butylamino benzamide) benzoic acid, 2-(2-octyl amino benzamide) benzoic acid, 2-(2-dodecyl amino benzamide) benzoic acid, 2-(2-cyclohexylamino benzamide) benzoic acid, 2-(2-(2-methylpropyl amino) benzamide) benzoic acid, 2-(2-(1-propyl butylamino) benzamide) benzoic acid, 2-(2-(3-methylbutyl amino) benzamide) benzoic acid, 2-(2-(1-methyl hexyl amino) benzamide) benzoic acid, 2-(2-(2-ethylhexyl amino) benzamide) benzoic acid, 2-(2-(2,2-dimethylpropyl amino) benzamide) benzoic acid, 2-(2-(3-phenylpropyl amino) benzamide) benzoic acid, 2-(2-(6-phenylhexyl amino benzamide) benzoic acid, 2-(2-[N-methyl-N-hexyl] amino benzamide) benzoic acid, 2-(2-iso indolyl benzamide) benzoic acid, 2-(2-butylamino benzamide)-4-nitrobenzoic acid, 2-(2-butylamino benzamide)-5-nitrobenzoic acid, 2-(2-butylamino benzamide)-5-trifluoromethyl benzoic acid, 2-(2-butylamino benzamide)-5-

hydroxybenzoic acid, 2-(2-butylamino benzamide)-5-methoxybenzoic acid, 2-(2-butylamino benzamide)-5-chlorobenzoic acid.

(0022)

2-(2-butylamino-4-phenethyl benzamide) benzoic acid, 2-(2-phenylamino-4-phenethyl benzamide) benzoic acid, 2-(2-butylamino-4-hexyl benzamide) benzoic acid, 2-(2-butylamino-4-decyl benzamide) benzoic acid, 2-(2-methylamino-4-phenylethenyl benzamide) benzoic acid, 2-(2-butylamino-4-phenylethenyl benzamide) benzoic acid, 2-(2-methylamino-4-benzyloxy benzamide) benzoic acid, 2-(2-butylamino-4-benzyloxy benzamide) benzoic acid, 2-(2-butylamino-4-cyclohexyl oxy benzamide) benzoic acid, 2-(2-butylamino-4-decyloxy benzamide) benzoic acid, 2-(2-(2-pyridyl) amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-thienyl) amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-furfuryl) amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-butylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-methylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-ethylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-propylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-octyl amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-decyl amino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-benzylamino-4-phenyl ethynyl benzamide) benzoic acid, 2-(2-(3-phenylpropyl) amino-4-phenyl ethynyl benzamide) benzoic acid.

(0023)

2-(2-methylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-ethylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-propylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-octyl amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-benzylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-phenylamino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-phenylamino-3-phenyl ethynyl benzamide) benzoic acid, 2-(2-(3-phenylpropyl) amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-hydroxyethyl) amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-mercaptoethyl) amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-amino ethyl) amino-5-phenyl ethynyl benzamide) benzoic acid, 2-(2-(2-(N,N-dimethylamino) ethyl) amino-5-phenyl ethynyl benzamide) benzoic acid.

(0024)

2-(2,6-dihexyl amino benzamide) benzoic acid, 2-(2,6-diphenylamino benzamide) benzoic acid, 5-hydroxy-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 5-methyl-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 5-bromo-2-(2-phenylamino-4-phenyl ethynyl benzamide)

benzoic acid, 5-methoxy-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 5-amino-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 5-mercapto-2-(2-phenylamino-4-phenyl ethynyl benzamide) benzoic acid, 3-(2-phenylamino-4-phenyl ethynyl benzamide) thiophene-2-carboxylic acid.

(0025)

5-methyl-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 5-bromo-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 5-methoxy-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 5-amino-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 5-mercapto-2-(2-phenylamino-4-benzyloxy benzamide) benzoic acid, 3-(2-phenylamino-4-benzyloxy benzamide) thiophene-2-carboxylic acid 2-(4-(1-octynyl)-2-phenylamino benzamide) benzoic acid, 2-(4-(1-pentynyl)-2-phenylamino benzamide) benzoic acid, 2-(4-(3,3-dimethylbutan-1-yl)-2-phenylamino benzamide) benzoic acid, 2-(2-butylamino-4-(3,3-dimethylbutan-1-yl) benzamide) benzoic acid, 2-(4-(3-cyclohexyl propan-1-yl)-2-phenylamino benzamide) benzoic acid, 2-(2-butylamino-4-(3,3-dimethylbutan-1-yl) benzamide) benzoic acid.

(0026)

2-(2-butylamino-4-(2-furfuryl) ethynyl benzamide) benzoic acid, 2-(2-phenylamino-5-(2-pyridyl) ethynyl benzamide) benzoic acid, 2-(2-phenylamino-5-(2-thienyl) ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-(3-methoxy propan-1-yl) benzamide) benzoic acid, 2-(2-butylamino-5-(3,3-diethoxy propan-1-yl) benzamide) benzoic acid, 2-(2-butylamino-5-(4-nitrophenyl) ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-(4-hydroxyphenyl) ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-(4-cyanophenyl) ethynyl benzamide) benzoic acid, 2-(2-butylamino-5-(4-aminophenyl) ethynyl benzamide) benzoic acid.

(0027)

4-benzyloxy-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide, 2-butylamino-4-phenyl ethynyl-N-(2-sulphamoyl phenyl) benzamide, 2-(2-pyridyl) amino-4-phenyl ethynyl-N-(2-sulphamoyl phenyl) benzamide, 2-butylamino-4-(3,3-dimethylbutan-1-yl)-N-(2-sulphamoyl phenyl) benzamide, 4-(3,3-dimethylbutan-1-yl)-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide, N-(2-(2-phenylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) acetamide, N-(2-(2-phenylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) butane amide, N-(2-(2-phenylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) pivalamide, 2-methyl-N-(2-(2-phenylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) propanamide, N-(2-(2-butylamino-4-phenyl ethynyl benzamide)

phenylsulfonyl) acetamide, N-(2-(2-butylamino-4-phenyl ethynyl benzamide) phenylsulfonyl) hexane amide.

(0028)

N-(2-(2-butylamino-4-(3,3-dimethylbutan-1-yl) benzamide) phenylsulfonyl) acetamide, N-(2-(2-butylamino-4-(3,3-dimethylbutan-1-yl) benzamide) phenylsulfonyl) pivalamide, N-(2-(4-(3,3-dimethylbutan-1-yl)-2-phenylamino benzamide) phenylsulfonyl) acetamide, N-(2-(4-(1-octynyl)-2-phenylamino benzamide) phenylsulfonyl) acetamide, N-(2-(2-butylamino-4-(1-octynyl) benzamide) phenylsulfonyl) acetamide, N-(2-(2-phenylamino-4-phenylethenyl benzamide) phenylsulfonyl) acetamide, N-(2-(4-(3,3-dimethylbutan-1-enyl)-2-phenylamino benzamide) phenylsulfonyl) acetamide, N-(2-(2-butylamino-4-(1-octynyl) benzamide) phenylsulfonyl) acetamide, N-(2-((2-methyl) propyl oxycarbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-((2,2-dimethyl) ethoxycarbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[phenyloxy carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[hexyloxy carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, 2-butylamino-N-((N-(2-methylpropyl) oxycarbonyl sulphamoyl) phenyl)-4-phenyl ethynyl benzamide, 2-butylamino-N-(2-[phenyloxy carbonyl sulphamoyl] phenyl)-4-phenyl ethynyl benzamide.

(0029)

N-(2-[methylamino carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-((2-methyl) propylamino carbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[phenylamino carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[butylamino carbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-[cyclohexyl aminocarbonyl sulphamoyl] phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-((1-piperidino) carbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide, N-(2-((4-methylpiperazino) carbonyl sulphamoyl) phenyl)-2-phenylamino-4-phenyl ethynyl benzamide.

(0030)

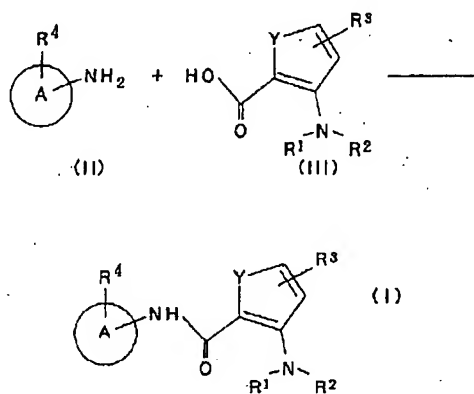
When acid functional group of R4 is free carboxylic acid, sulfonic acid or the like, aromatic amide derivative of this invention may be used as drug of this invention in a form of acid itself or in a form of pharmacologically acceptable salt thereof. As such salts, conventionally used non-toxic salt, salt with inorganic base, for example alkali metal salt (for example sodium salt, potassium salt), alkaline earth metal salt (for example calcium salt, magnesium salt), ammonium salt, salt with organic base, for example organic amine salt (for example triethylamine salt, pyridine salt, picoline salt,

ethanolamine salt, triethanolamine salt, N,N-dimethylaminoethyl amine salt) or salt with basic amino acid and the like are nominated.

(0031)

Aromatic amide derivative of this invention can be produced according to for example following process. If a such process for the production is shown with chemical formula, it is summarised as follows.

(0032)



(0033)

In the formula, R¹, R², R³, R⁴, Y and ring A have the aforesaid meanings. In other words, aromatic amide derivative of this invention can be produced basically by condensing amino compound represented by formula (II) corresponding to the target compound of formula (I) and carboxylic acid compound represented by formula (III).

(0034)

This condensation reaction can be performed in the presence of condensing agent, and as condensing agent, it is possible to use for example carbodiimide reagent such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and the like, carbonyldiimidazole, 2-chloro-1-methylpyridinium iodide salt.

(0035)

Moreover, it can be carried out by the method wherein carboxylic acid compound represented by formula (III) is converted into corresponding acid halide by the reaction with halogenation reagent such as thionyl chloride or phosphorus pentachloride and the like, or it is converted into an acid

anhydride which is a reactive body by using for example p-toluenesulfonic acid chloride, chlorocarbonic acid ethyl, pivaloyl chloride and the like, and thereafter caused to react with amino compound represented by formula (II).

(0036)

Moreover, as for this condensation reaction, it is possible to use a suitable solvent which is selected from inert solvent, for example ethers such as diethyl ether, tetrahydrofuran, dioxane and the like, aromatic hydrocarbon such as benzene, toluene, xylene and the like, hydrocarbon such as cyclopentane, cyclohexane and the like, halogenated hydrocarbon such as dichloro methane, dichloro ethane, trichloroethane, chloroform and the like, nitriles such as acetonitrile, propionitrile and the like, esters such as ethyl acetate and the like, N,N-dimethylformamide, dimethylsulfoxide and the like.

(0037)

Moreover, this condensation reaction can be performed in the presence of a base. As base, organic or inorganic base is nominated, for example alkali metal hydride such as sodium hydride, potassium hydride and the like, alkali metal hydroxide such as sodium hydroxide, potassium hydroxide and the like, alkali metal (or earth metal) carbonate such as sodium carbonate, potassium carbonate, magnesium carbonate, calcium carbonate and the like, alkali metal hydrogencarbonate such as sodium bicarbonate, potassium bicarbonate and the like, alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium tertiary butoxide and the like, trialkylamine such as trimethylamine, triethylamine, N,N-diisopropyl-N-ethylamine and the like, pyridine compound such as pyridine, dimethylaminopyridine, picoline, lutidine and the like. The quantity of base, 1-10 times equivalent with respect to carboxylic acid compound is preferred.

(0038)

In this condensation reaction, the quantity of each of amino compound of formula (II) and carboxylic acid of formula (III) used is preferably almost equimolar amount. Moreover, the reaction temperature and the reaction time are not restricted, in particular depending on a kind of compound of formula (II) and (III) to be reacted, and the target compound can be obtained in a good yield by reacting for about 0.1-25 hours under the temperature condition of about 0 degrees to about boiling point of solvent used. Moreover, the quantity of use of condensing agent is preferably added 1-10 times equivalent with respect to compound of formula (II) and (III) to be reacted.

(0039)

On the other hand, in aromatic amide derivative represented by the aforesaid general formula (I) obtained by aforesaid condensation reaction, when substituent R₄ is carboxylate ester, it can be derived to free carboxylic acid by ordinary ester hydrolysis reaction for example reaction with alkali such as sodium hydroxide solution, potassium hydroxide solution or the like in alcohol system solvent such as methanol, ethanol, propanol and the like. Moreover, in aromatic amide derivative represented by the aforesaid general formula (I), the compound in which substituent R₄ is acyl sulfonamide group can be derived by reacting for example the compound in which substituent R₄ of aromatic amide derivative represented by formula (I) obtained in above-mentioned condensation reaction is sulfonamide group with acyl halide in the presence of aforesaid suitable base in the aforesaid inert solvent.

(0040)

The target aromatic amide derivative represented by aforesaid general formula (I) can be obtained by suitably combining these aforesaid reactions, and in accordance with requirements, reaction solution can be isolated and purified by subjecting purification technique carried out usually, for example filtration, decantation, extraction, washing, solvent elimination by distillation, column or thin layer chromatography, recrystallisation, distillation and the like.

(0041)

When aromatic amide derivative or a pharmacologically acceptable salt thereof represented by the aforesaid general formula (I) of this invention is administered in a human as drug, although the dosage is different depending on the age or symptom of target disease, but preferably, it is orally-administered an effective dose, for example usually 5-30 mg per day divided into 1-3. It is possible that the drug of this invention is made formed into various kinds of pharmaceutical forms, oral administration formulation such as tablet, encapsulated formulation, granule, powder, troche agent, liquid agent and the like. These formulation can be carried out by itself familiar processed. For example, tablet, encapsulated formulation, granule, powder, troche agent and the like can be produced by formulating the compound of formula (I) of this invention by suitably combining with excipient such as starch, mannitol, lactose or the like, bonding agent such as carboxymethylcellulose sodium, hydroxypropylcellulose and the like, disintegrating agent such as crystalline cellulose, carboxymethylcellulose and the like, lubricant such as talc, magnesium stearate and the like, flowability improver such as light anhydrous silicic acid and the like, or the like.

(0042)

Moreover, drug of this invention can be formed into injection. This is pharmaceutically formulated, and for example, it is solubilised or dispersed in aqueous carrier such as physiological saline or the like, using detergent and dispersant and the beforehand, or moreover when required, injectable crystal formulation or lyophilization formulation is prepared, and solution or dispersion can be prepared at the time of use. A pH regulating agent and stabilising agent may be added as arbitrary component to aforesaid aqueous carrier. Dose and administration route of such injection are not restricted in particular, and the condition and characteristic of patient are taken into account, and a necessary dose can be administered safely by using intravenous drip infusion and also intraarterial, subcutaneous or intraperitoneal injection and the like.

(0043)

Examples

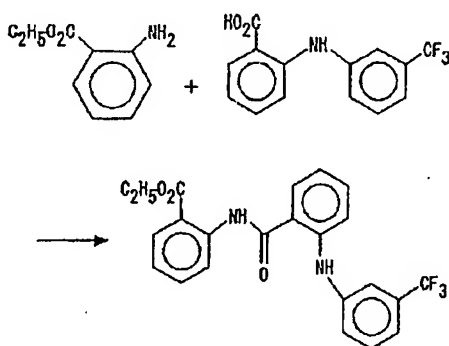
Below this invention is described in further detail by Reference Example, Example and Pharmacological Test Example. However, in the this invention, there are not any restrictions in any way by following description.

(0044)

Reference Example 1

2-(2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid ethyl ester.

(0045)



(0046)

Thionyl chloride 2.0 ml and several drops of N,N-dimethylformamide were added to anhydrous benzene solution (20 ml) of 2-(3-trifluoromethylphenyl amino) benzoic acid 1.5 g (5.33 mmol), and the mixture was heated under reflux for two hours. It was cooled to room temperature, and next

excess thionyl chloride was eliminated by distillation under reduced pressure, and the residue was dissolved in benzene 10 ml, and under reduced pressure solvent was eliminated by distillation once again. The residue was dissolved in ethyl acetate 15 ml, and this was dropwise-added under ice cooling to mixed solution of 10 ml of ethyl acetate and 15 ml of water of potassium carbonate 1.30 g (10.67 mmol) and 2-ethyl aminobenzoic acid 0.78 ml (5.33 mmol) and was stirred at room temperature for four hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and next the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 1.82 g (yield 80.1 %) were obtained.

(0047)

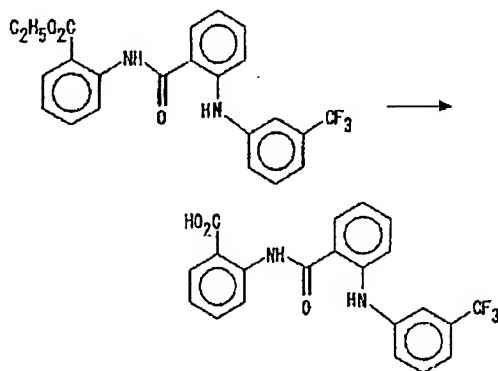
NMR (CDCl₃) delta: 1.43 (3H, t, J = 7 Hz), 4.42 (2H, q, J = 7 Hz), 6.98 (1H, ddd, J = 8 Hz, 6 Hz, 2 Hz), 7.14 (1H, t, J = 8 Hz), 7.19-7.26 (1H, m), 7.34-7.44 (4H, m), 7.47 (1H, s), 7.60 (1H, dt, J = 8 Hz, 1 Hz), 7.84 (1H, d, J = 8 Hz), 8.11 (1H, dd, J = 8 Hz, 1 Hz), 8.79 (1H, d, J = 8 Hz), 9.76 (1H, s), 12.00 (1H, s).

(0048)

Example 1

2-(2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid.

(0049)



(0050)

1N-sodium hydroxide solution 15 ml were added to ethanol solution (15 ml) of 2-(2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid ethyl ester 0.66 g produced in Reference

Example 1 (1.54 mmol), and the mixture was heated under reflux for two hours. It was cooled to room temperature, and ethanol was eliminated by distillation under reduced pressure, and the residue was extracted with ether. The organic layer was washed successively with 1N-hydrochloric acid and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and next the solvent was concentrated under reduced pressure. The residue was recrystallised from ether-hexane, and title compound 0.44 g (yield 71.6 %) were obtained.

(0051)

NMR (CDCl₃) delta: 6.96 (1H, ddd, J = 8 Hz, 6 Hz, 2 Hz), 7.15-7.29 (2H, m), 7.35-7.45 (4H, m), 7.48 (1H, s), 7.68 (1H, dt, J = 8 Hz, 1 Hz), 7.79 (1H, d, J = 8 Hz), 8.19 (1H, d, J = 8 Hz), 8.83 (1H, d, J = 8 Hz), 9.70 (1H, s), 11.73 (1H, s).

IR (ν, cm⁻¹, KBr): 3500-2600, 1708, 1652, 1612, 1582, 1456, 1336, 1210, 1112, 752, 740 MS (m/z, %): 400 (M⁺, 50), 382 (6), 263 (100), 264 (48).

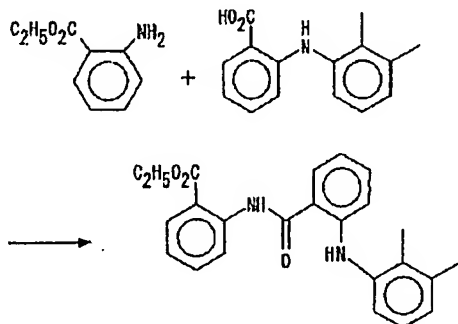
mp: 189-192 degrees.

(0052)

Reference Example 2

2-(2-(2,3-dimethyl phenylamino) benzamide) benzoic acid ethyl ester.

(0053)



(0054)

Thionyl chloride 2.0 ml and several drops of N,N-dimethylformamide were added to anhydrous benzene solution (20 ml) of 2-(2,3-dimethyl phenylamino) benzoic acid 2.0 g (8.29 mmol), and the mixture was heated under reflux for two hours. It was cooled to room temperature, and next excess thionyl chloride was eliminated by distillation under reduced pressure, and the residue was dissolved in benzene 10 ml, and under reduced pressure solvent was eliminated by distillation once again. The

residue was dissolved in ethyl acetate 10 ml, and this was dropwise-added under ice cooling to mixed solution of ethyl acetate (10 ml) and 15 ml of water containing potassium carbonate 2.1 g (17.41 mmol) and 2-ethyl aminobenzoic acid 1.2 ml (8.29 mmol) and was stirred at room temperature for three hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and next the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 1.3 g (yield 40.4 %) were obtained.

(0055)

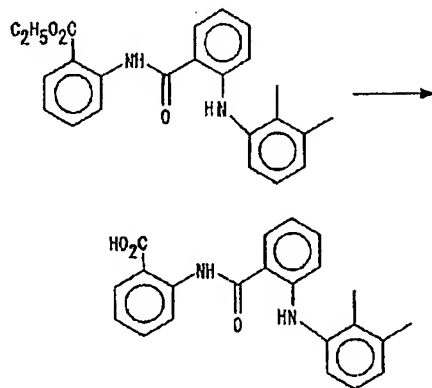
NMR (CDCl₃) delta: 1.44 (3H, t, J = 7 Hz), 2.22 (3H, s), 2.33 (3H, s), 4.43 (2H, q, J = 7 Hz), 6.81 (1H, dt, J = 7 Hz, 1 Hz), 6.88 (1H, d, J = 8 Hz), 6.98 (1H, d, J = 7 Hz), 7.04-7.30 (4H, m), 7.59 (1H, dt, J = 8 Hz, 1 Hz), 7.82 (1H, dd, J = 8 Hz, 1 Hz), 8.11 (1H, dd, J = 8 Hz, 1 Hz), 8.83 (1H, d, J = 8 Hz), 9.48 (1H, s), 11.96 (1H, s).

(0056)

Example 2

2-(2-(2,3-dimethyl phenylamino) benzamide) benzoic acid.

(0057)



(0058)

1N-sodium hydroxide 15 ml were added to methanol solution (15 ml) of 2-(2-(2,3-dimethyl phenylamino) benzamide) benzoic acid ethyl ester 0.61 g (1.84 mmol) produced in Reference Example 2, and the mixture was heated under reflux for three hours. It was cooled to room

temperature, and methanol was eliminated by distillation under reduced pressure, and the residue was extracted with ether. The organic layer was washed successively with 1N-hydrochloric acid and saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and next the solvent was concentrated under reduced pressure. The residue was recrystallised from ether-hexane, and title compound 0.34 g (yield 60.2 %) were obtained.

(0059)

NMR (CDCl₃) delta: 2.22 (3H, s), 2.33 (3H, s), 6.79 (1H, t, J = 8 Hz), 6.89 (1H, d, J = 8 Hz), 6.99 (1H, d, J = 7 Hz), 7.09 (1H, t, J = 8 Hz), 7.13-7.22 (2H, m), 7.23-7.31 (1H, m), 7.67 (1H, dt, J = 8 Hz, 1 Hz), 7.76 (1H, d, J = 7 Hz), 8.19 (1H, dd, J = 8 Hz, 1 Hz), 8.87 (1H, d, J = 8 Hz), 9.43 (1H, s), 11.69 (1H, s).

IR (ν, cm⁻¹, KBr): 3380, 3500-2400, 1696, 1646, 1582, 1294, 1254, 1212, 754, 650 MS (m/z, %): 360 (M⁺, 58), 342 (8), 223 (100), 224 (43).

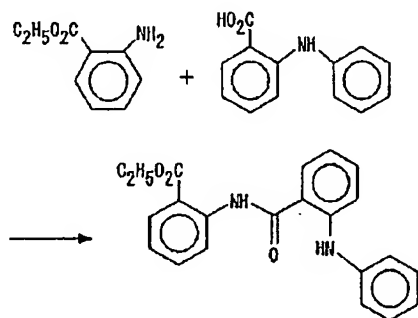
mp: 107-108 degrees.

(0060)

Reference Example 3

2-(2-phenylamino benzamide) benzoic acid ethyl ester.

(0061)



(0062)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide were added to anhydrous benzene solution (10 ml) of 2-phenylamino benzoic acid 0.50 g (2.34 mmol) and were heated under reflux for two hours, and the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in benzene 10 ml, and solvent was eliminated under reduced pressure by distillation once again. The residue was dissolved in ethyl acetate 10 ml, and this was dropwise-

added under ice cooling to mixed solution of ethyl acetate 10 ml and 15 ml of water containing potassium carbonate 0.65 g (4.69 mmol) and 2-ethyl aminobenzoic acid 0.34 ml (2.25 mmol) and was stirred at room temperature for 18 hours. Thereafter, the organic layer was washed successively with water, 1N-hydrochloric acid, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. It was purified by silica gel column chromatography, and title compound 0.36 g (yield 42.2 %) were obtained.

(0063)

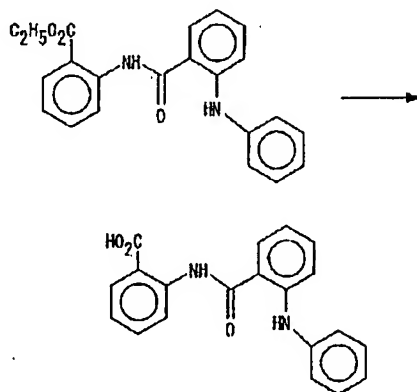
NMR (CDCl₃) delta: 1.43 (3H, t, J = 7 Hz), 4.42 (2H, q, J = 7 Hz), 6.88 (1H, dt, J = 7 Hz, 1 Hz), 7.03 (1H, t, J = 7 Hz), 7.12 (1H, t, J = 7 Hz), 7.20-7.43 (6H, m), 7.59 (1H, dt, J = 8 Hz, 1 Hz), 7.81 (1H, d, J = 8 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, d, J = 8 Hz), 9.63 (1H, s), 11.94 (1H, s).

(0064)

Example 3

2-(2-phenylamino benzamide) benzoic acid.

(0065)



(0066)

1N sodium hydroxide 15 ml were added to methanol solution of 2-(2-phenylamino benzamide) benzoic acid ethyl ester 0.14 g (0.337 mmol) produced in Reference Example 3 and were heated under reflux for two hours. Methanol was eliminated by distillation under reduced pressure and was washed with ether. Concentrated hydrochloric acid was dropwise-added under ice cooling to the aqueous layer, and it was acidified, and next it was extracted twice with acetic acid ethyl ester. The

organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 0.10 g (yield 74.2 %) were obtained.

(0067)

NMR (DMSO-d₆) delta: 6.91-7.04 (2H, m), 7.15-7.26 (3H, m), 7.26-7.37 (3H, m), 7.42 (1H, dt, J = 8 Hz, 1 Hz), 7.65 (1H, dt, J = 8 Hz, 1 Hz), 7.78 (1H, d, J = 7 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 9.30 (1H, s), 12.01 (1H, s).

IR (ν, cm⁻¹, KBr): 3372, 3400-2700, 1696, 1646, 1584, 1504, 1452, 1210, 750 MS (m/z, %): 332 (M⁺, 58), 314 (5), 195 (100), 223 (14), 196 (50), 167 (30).

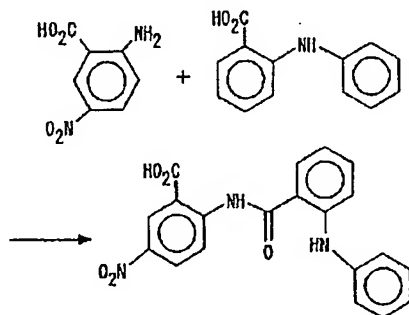
mp: 239-240 degrees.

(0068)

Example 4

5-nitro-2-(2-phenylamino benzamide) benzoic acid.

(0069)



(0070)

Thionyl chloride 0.26 ml (3.51 mmol) were added to anhydrous benzene solution (10 ml) of 2-phenylamino benzoic acid 0.50 g (2.34 mmol) and were stirred with room temperature for two hours, and under reduced pressure solvent was eliminated by distillation. Methylene chloride solution of the residue (10 ml) was dropwise-added under ice cooling to 2-amino-5-nitrobenzoic acid 427 mg (2.34 mmol) and methylene chloride (100 ml) solution of triethylamine 0.65 ml (4.68 mmol) and was stirred at room temperature for 18 hours. The organic layer was washed successively with water, 1N-hydrochloric acid and saturated aqueous sodium chloride solution, and it was dried with anhydrous

sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. It was purified by silica gel column chromatography, and title compound 300 mg (yield 34 %) were obtained.

(0071)

NMR (CDCl₃) delta: 6.95-7.01 (2H, m), 7.17 (2H, d, J = 7 Hz), 7.28-7.34 (3H, m), 7.45 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.79 (1H, d, J = 7 Hz), 8.49 (1H, dd, J = 7 Hz, 2 Hz), 7.76 (1H, d, J = 7 Hz), 8.76 (1H, d, J = 2 Hz), 8.86 (1H, dd, J = 7 Hz, 2 Hz), 9.20 (1H, br-s), 12.41 (1H, br-s).

IR (v, cm⁻¹, KBr): 1706, 1646, 1598, 1574, 1556, 1498, 1450, 1346, 1286, 1254.

EI-MS (m/z, %): 377 (M⁺, 48), 347 (II), 197 (10), 196 (78), 168 (8).

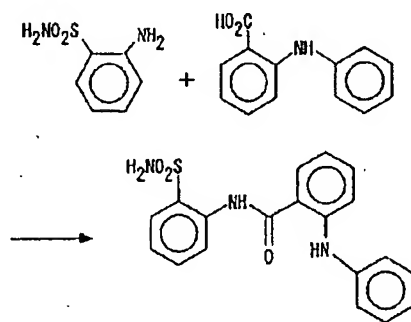
mp: 232-233 degrees.

(0072)

Example 5

2-phenylamino-N-(2-sulphamoyl phenyl) benzamide.

(0073)



(0074)

Thionyl chloride 0.26 ml (6.9 mmol) were added to anhydrous benzene solution (10 ml) of 2-phenylamino benzoic acid 1 g (4.6 mmol) and were stirred with room temperature for two hours, and under reduced pressure solvent was eliminated by distillation. Methylene chloride solution of the residue (10 ml) was dropwise-added under ice cooling in pyridine (10 ml) solution of 2-aminobenzene sulfonamide 808 mg (4.6 mmol) and was stirred at room temperature for 18 hours, and methylene chloride was eliminated by distillation. The residue was extracted with ethyl acetate, and it was washed successively with water, 1N-hydrochloric acid and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was

eliminated by distillation under reduced pressure. It was purified by silica gel column chromatography, and title compound 1.2 g (yield 70 %) were obtained.

(0075)

NMR (CDCl₃) delta: 4.89 (2H, br-s), 6.86 (1H, ddd, J = 6 Hz, 6 Hz, 1 Hz), 7.06 (1H, ddd, J = 6 Hz, 6 Hz, 1 Hz), 7.21-7.30 (7H, m), 7.63 (1H, dd, J = 6 Hz, 6 Hz), 7.67 (1H, d, J = 6 Hz), 7.97 (1H, d, J = 6 Hz), 8.40 (1H, d, J = 6 Hz), 9.49 (1H, br-s), 9.87 (1H, br-s).

IR (ν, cm⁻¹, KBr): 1644, 1580, 1516, 1506, 1472, 1414, 1332, 1290, 1258, 1222, 1168, 1156.

El-MS (m/z, %): 367 (M⁺, 52), 236 (17), 196 (65), 195 (100), 167 (37).

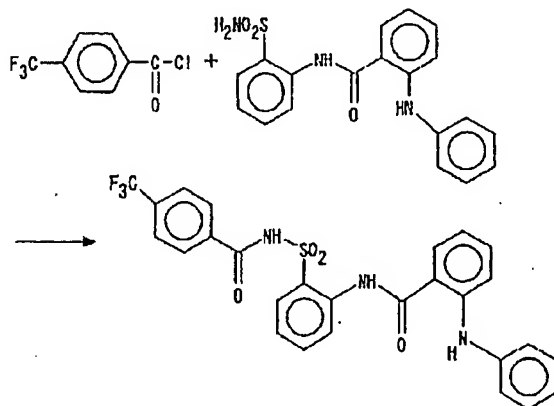
mp: 126-127 degrees.

(0076)

Example 6

N-(2-(4-benzyloxy-2-phenyl amino benzoamide) benzene sulphonyl) benzamide.

(0077)



(0078)

4-benzyloxy-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 300 mg (0.82 mmol) produced in Example 5, 4-trifluoromethyl benzoyl chloride 0.24 ml (1.64 mmol) and water-dioxane 1=1 solution (10 ml) of potassium carbonate 340 mg (2.4 mmol) were stirred for 18 hours. The solvent was eliminated by distillation, and the residue was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. It was purified by silica gel column chromatography, and title compound 200 mg (yield 45 %) were obtained.

(0079)

NMR (CDCl₃) delta: 6.92 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.00 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.17 (2H, d, J = 7 Hz), 7.29-7.45 (5H, m), 7.64-7.70 (3H, m), 7.95 (1H, dd, J = 7 Hz, 1 Hz), 7.96-8.10 (3H, m), 8.23 (1H, d, J = 7 Hz), 9.40 (1H, br-s), 10.65 (1H, br-s).

IR (ν, cm⁻¹, KBr): 1696, 1662, 1644, 1580, 1518, 1474, 1452, 1324, 1288.

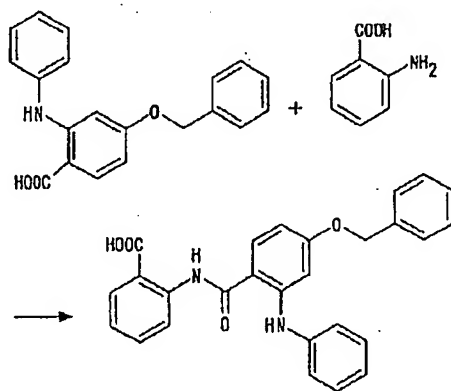
EI-MS (m/z, %): 539 (M⁺, 25), 288 (6), 197 (7), 196 (57), 195 (100), 173 (9), 169 (8).

(0080)

Example 7

2-(4-benzyloxy-2-phenylamino benzamide) benzoic acid.

(0081)



(0082)

Thionyl chloride 0.04 ml (0.50 mmol) were added under a nitrogen atmosphere in methylene chloride (10 ml) solution of 2-phenylamino-4-benzyloxy benzoic acid 100 mg (0.31 mmol), and it was stirred for one hour at room temperature, and next the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in methylene chloride 10 ml, and this was dropwise-added under ice cooling to triethylamine 0.2 ml (1.30 mmol), methylene chloride (10 ml) solution of 2-aminobenzoic acid 0.04 g (0.31 mmol) and was stirred at room temperature for 18 hours. 1N-hydrochloric acid was added, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by

distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 38 mg (yield 27.7 %) were obtained.

(0083)

NMR (CDCl₃) delta: 5.04 (2H, s), 6.49 (1H, dd, J = 9 Hz, 2 Hz), 6.86 (1H, d, J = 2 Hz), 7.05 (1H, t, J = 7 Hz), 7.11-7.18 (3H, m), 7.25-7.42 (7H, m), 7.64 (1H, dt, J = 8 Hz, 1 Hz), 7.73 (1H, d, J = 9.0 Hz), 8.15 (1H, dd, J = 8 Hz, 1 Hz), 8.81 (1H, d, J = 8 Hz), 9.93 (1H, s), 11.64 (1H, s).

IR (v, cm⁻¹, KBr): 3500-2500, 1682, 1652, 1580, 1524, 1452, 1254, 752.

EI-MS (m/z, %): 438 (M⁺, 20), 420 (43), 302(11), 301 (16), 211 (9), 91 (100).

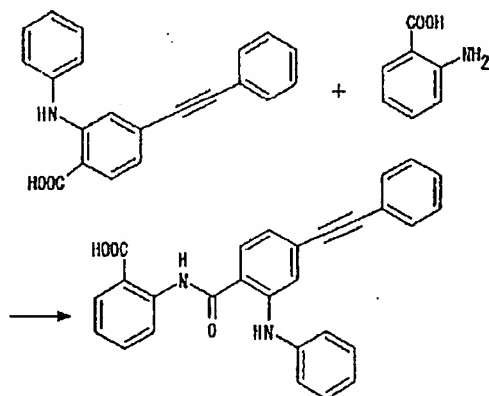
mp: 203-204 degrees.

(0084)

Example 8

2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0085)



(0086)

Thionyl chloride 0.15 ml (1.90 mmol) were added under a nitrogen atmosphere to methylene chloride (10 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 200 mg (0.64 mmol), and it was stirred for one hour at room temperature, and next the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in methylene chloride 10 ml, and this was dropwise-added under ice cooling to triethylamine 0.36 ml (2.55 mmol), methylene chloride (10 ml) solution of 2-aminobenzoic acid 0.09 g (0.64 mmol) and was stirred at room temperature for 18 hours. 1N-hydrochloric acid was added, and extraction was carried out with acetic acid ethyl ester.

The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and thereafter, it was recrystallised with acetonitrile, and title compound 37 mg (yield 13.4 %) were obtained.

(0087)

NMR (DMSO-d₆) delta: 7.06 (1H, t, J = 7 Hz), 7.11 (1H, dd, J = 8 Hz, 1 Hz), 7.19-7.27 (3H, m), 7.32-7.46 (6H, m), 7.54-7.60 (2H, m), 7.65 (1H, dt, J = 8 Hz, 1 Hz), 7.82 (1H, d, J = 8 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.57 (1H, d, J = 8 Hz), 9.36 (1H, s), 12.08 (1H, s)

IR (ν, cm⁻¹, KBr): 3324, 3400-2300, 1682, 1650, 1582, 1556, 1416, 1266, 756.

EI-MS (m/z, %): 432 (M⁺, 23), 414 (100), 295 (55), 188 (65), 187 (58).

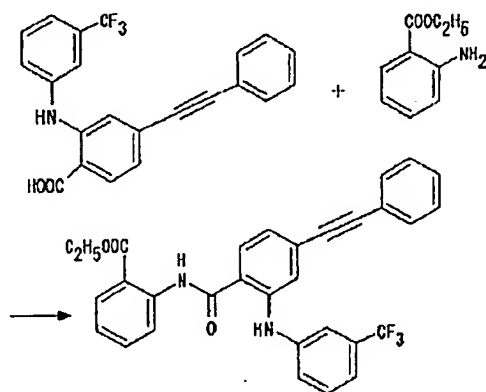
mp: 220-223 degrees.

(0088)

Reference Example 4

2 (4-phenyl-ethynyl-2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid ethyl ester.

(0089)



(0090)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide were added to anhydrous benzene solution (10 ml) of 4-phenyl-ethynyl-2-(3-trifluoro phenylamino) benzoic acid 250 mg (0.66 mmol), and the mixture was heated under reflux for two hours. It was cooled to room temperature, and next excess thionyl chloride was eliminated by distillation under reduced pressure. The residue

was dissolved in benzene 10 ml, and solvent was eliminated under reduced pressure by distillation once again. The residue is dissolved in ethyl acetate 10 ml. Mixed solution of 10 ml of ethyl acetate and 15 ml of water containing potassium carbonate 0.18 g (1.31 mmol) and 2-ethyl aminobenzoic acid 0.1 ml (0.66 mmol) was dropwise-added under ice cooling to this, and it was stirred at room temperature for 20 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water, 1N-hydrochloric acid, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation. It was purified by silica gel column chromatography, and title compound 0.10 g (yield 29.4 %) were obtained.

(0091)

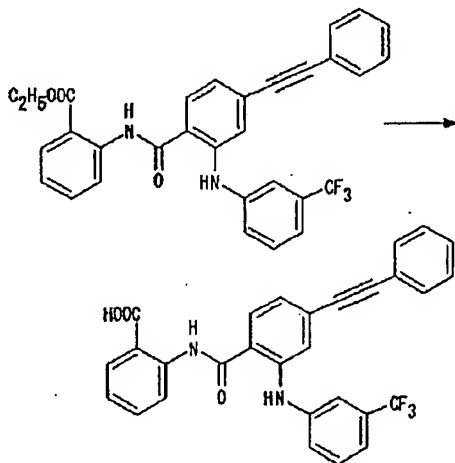
NMR (DMSO-d₆) delta: 1.44 (3H, t, J = 7 Hz), 4.43 (2H, q, J = 7 Hz), 7.10 (1H, dd, J = 8 Hz, 1 Hz), 7.15 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.27-7.30 (1H, m), 7.33-7.37 (3H, m), 7.42-7.54 (6H, m), 7.61 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.81 (1H, d, J = 8 Hz), 8.12 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 9.83 (1H, s), 12.05 (1H, s).

(0092)

Example 9

2-(4-phenyl-ethynyl-2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid.

(0093)



(0094)

1N-sodium hydroxide solution 10 ml were added to ethanol (10 ml) solution of 2-(4-phenyl-ethynyl-2-(3-trifluoromethylphenyl amino) benzamide) benzoic acid ethyl ester 100 mg (0.15 mmol) produced in Reference Example 4, and the mixture was heated under reflux for two hours. Ethanol was eliminated by distillation under reduced pressure, and the residue was neutralised at concentrated hydrochloric acid, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised at acetonitrile, and perform, title compound 75 mg (yield 77.6 %) were obtained.

(0095)

NMR (DMSO-d₆) delta: 7.17-7.28 (3H, m), 7.38-7.54 (7H, m), 7.54-7.65 (3H, m), 7.82 (1H, d, J = 8 Hz), 8.01 (1H, dd, J = 8 Hz, 1 Hz), 8.55 (1H, d, J = 8 Hz), 9.28 (1H, s), 12.06 (1H, s).

IR (ν, cm⁻¹, KBr): 3304, 3500-2400, 1654, 1608, 1538, 1418, 1334, 1256, 1226, 1128, 754.

EI-MS (m/z, %): 484 (M⁺, 12), 483 (34), 482 (100), 464 (12), 363 (12), 256 (27), 213 (13).

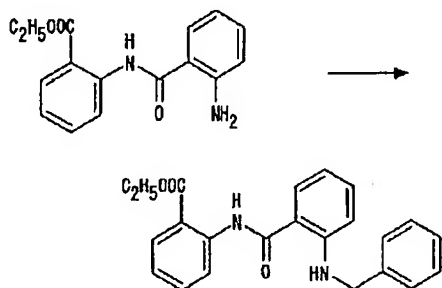
mp: 228-230 degrees.

(0096)

Reference Example 5

2-(2-benzylamino benzamide) benzoic acid ethyl ester.

(0097)



(0098)

Potassium carbonate 0.76 g (5.54 mmol) and benzyl bromide 0.6 ml (5.54 mmol) were added to N, N-dimethylformamide (20 ml) solution of 2-amino benzamide benzoic acid ethyl ester 1.5 g (5.28 mmol), and the mixture was stirred at room temperature for 18 hours. Water was added to the

reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 968 mg (yield 49.0 %) were obtained.

(0099)

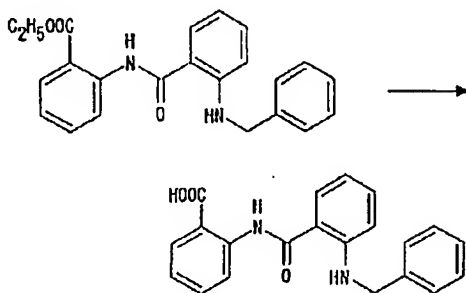
NMR (CDCl₃) delta: 1.43 (3H, t, J = 7 Hz), 4.41 (2H, q, J = 7 Hz), 4.46 (2H, d, J = 6 Hz), 6.67 (1H, d, J = 8 Hz), 6.92 (1H, dt, J = 7 Hz, 1 Hz), 7.10 (1H, dt, J = 7 Hz, 1 Hz), 7.22-7.41 (6H, m), 7.57 (1H, dt, J = 8 Hz, 1 Hz), 7.78 (1H, dd, J = 8 Hz, 1 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.30-8.43 (1H, m), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.88 (1H, s).

(0100)

Example 10

2-(2-benzylamino benzamide) benzoic acid.

(0101)



(0102)

1N-sodium hydroxide solution 15 ml were added to 2-(2-benzylamino benzamide) benzoic acid ethyl ester 400 mg (1.07 mmol) ethanol solution (15 ml) produced in Reference Example 5, and the mixture was heated under reflux for three hours. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation. The residue was recrystallised using ether / hexane, and title compound 273 mg (yield 73.7 %) were obtained.

(0103)

NMR (CDCl₃) delta: 4.47 (2H, s), 6.66-6.72 (2H, m), 7.14 (1H, dt, J = 8 Hz, 1 Hz), 7.22-7.41 (7H, m), 7.64 (1H, dt, J = 8 Hz, 1 Hz), 7.73 (1H, dd, J = 8 Hz, 1 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.81 (1H, dd, J = 8 Hz, 1 Hz), 11.63 (1H, s).

IR (v, cm⁻¹, KBr): 3404, 3500-2800, 1698, 1644, 1610, 1516, 1452, 1362, 1212, 756.

EI-MS (m/z, %): 346 (M⁺, 80), 328 (19), 210 (79), 209 (80), 181 (80), 180 (90), 91 (100).

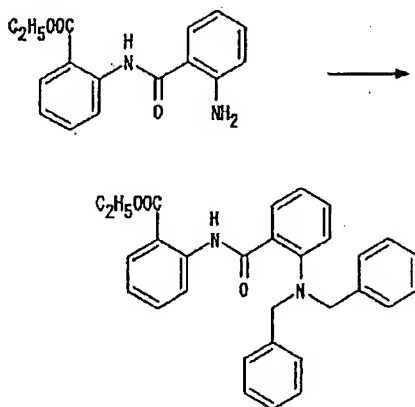
mp: 175-176 degrees.

(0104)

Reference Example 6

2-(2-dibenzylamino benzamide) benzoic acid ethyl ester.

(0105)



(0106)

Potassium carbonate 1.52 g (11.08 mmol) and benzyl bromide 1.3 ml (11.08 mmol) were added to N, N-dimethylformamide (20 ml) solution of 2-amino benzamide benzoic acid ethyl ester 1.5 g (5.28 mmol), and the mixture was stirred at room temperature for 18 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 1.08 mg (yield 44.0 %) were obtained.

(0107)

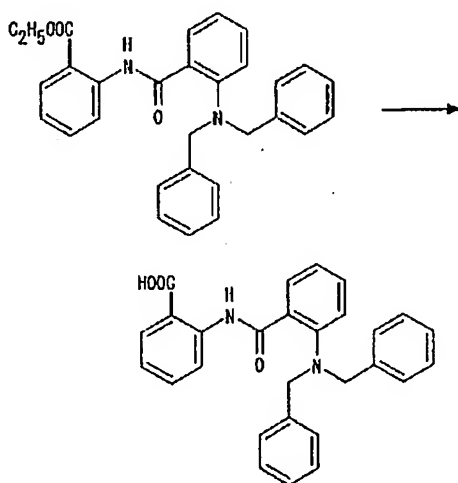
NMR (CDCl₃) delta: 1.33 (3H, t, J = 7 Hz), 4.28 (2H, q, J = 7 Hz), 4.29 (4H, s), 6.87 (1H, dd, J = 8 Hz, 1 Hz), 7.06 (1H, dt, J = 8 Hz, 1 Hz), 7.11-1.21 (11H, m), 7.58 (1H, dd, J = 8 Hz, 1 Hz), 7.74 (1H, dd, J = 8 Hz, 1 Hz), 8.07 (1H, dd, J = 8 Hz, 1 Hz), 8.82 (1H, dd, J = 8 Hz, 1 Hz), 11.88 (1H, s).

(0108)

Example 11

2-(2-dibenzylamino benzamide) benzoic acid.

(0109)



(0110)

1N-sodium hydroxide solution 10 ml were added to 2-(2-dibenzylamino benzamide) benzoic acid ethyl ester 750 mg (1.61 mmol) ethanol solution (10 ml) produced in Reference Example 6, and the mixture was heated under reflux for three hours. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was distilled under reduced pressure. The residue was recrystallised using ethyl acetate / hexane, and title compound 590 mg (yield 84.0 %) were obtained.

(0111)

NMR (CDCl₃) delta: 4.27 (4H, s), 6.86 (1H, dd, J = 8 Hz, 1 Hz), 7.07 (1H, dt, J = 8 Hz, 1 Hz), 7.11-7.22 (10H, m), 7.63 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.80 (1H, dd, J = 8 Hz, 1 Hz), 8.06 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.08 (1H, s).

IR (ν, cm⁻¹, KBr): 3500-2700, 1718, 1636, 1506, 1452, 1288, 1180, 1164, 762, 698.

EI-MS (m/z, %): 436 (M⁺, 1), 435 (4), 346 (24), 345 (86), 327 (18), 209 (37), 208 (100), 91 (80).

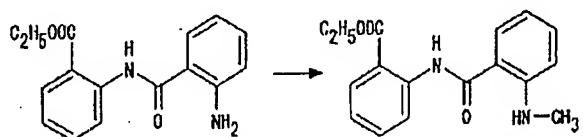
mp: 147-148 degrees.

(0112)

Reference Example 7

2-(methylaminobenzamide) benzoic acid ethyl ester.

(0113)



(0114)

Potassium carbonate 0.5 g (3.70 mmol) and iodomethane 0.3 ml (3.70 mmol) were added to N, N-dimethylformamide (10 ml) solution of 2-amino benzamide benzoic acid ethyl ester 1.0 g (3.52 mmol), and the mixture was stirred at room temperature for 16 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 310 mg (yield 29.5 %) were obtained.

(0115)

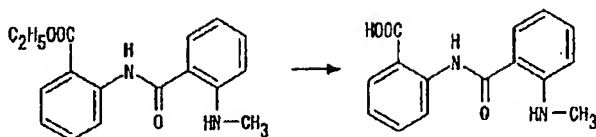
NMR (CDCl₃) delta: 1.42 (3H, t, J = 7 Hz), 2.91 (3H, d, J = 5 Hz), 4.41 (2H, q, J = 7 Hz), 6.69-6.74 (2H, m), 7.09 (1H, dt, J = 8 Hz, 1 Hz), 7.38 (1H, dt, J = 8 Hz, 1 Hz), 7.57 (1H, dt, J = 8 Hz, 1 Hz), 7.75 (1H, dd, J = 8 Hz, 1 Hz), 7.82 (1H, s), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.84 (1H, s).

(0116)

Example 12

2-(2-methylaminobenzamide) benzoic acid.

(0117)



(0118)

1N-sodium hydroxide solution 6 ml were added to 2-(2-methylaminobenzamide) benzoic acid ethyl ester 95 mg (0.32 mmol) ethanol solution (6 ml) produced in Reference Example 7, and the mixture was heated under reflux for one hour. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was distilled under reduced pressure. The residue was recrystallised using ether / hexane, and title compound 80 mg (yield 93.1 %) were obtained.

(0119)

NMR (CDCl₃) delta: 2.83 (3H, s), 6.67 (1H, dt, J = 8 Hz, 1 Hz), 7.18 (1H, dt, J = 8 Hz, 1 Hz), 7.40 (1H, dt, J = 8 Hz, 1 Hz), 7.60-7.70 (3H, m), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.62 (1H, dd, J = 8 Hz, 1 Hz), 11.96 (1H, s), 13.71 (1H, br-s).

IR (ν, cm⁻¹, KBr): 3424, 3400-2500, 1690, 1642, 1608, 1522, 1452, 1296, 1214, 752.

EI-MS (m/z, %): 270 (M⁺, 60), 252 (6), 134 (100), 105 (16), 91 (30), 77 (33).

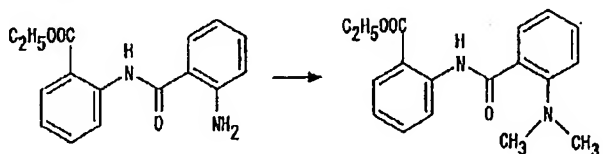
mp: 205-207 degrees.

(0120)

Reference Example 8

2-(dimethylamino benzamide) benzoic acid ethyl ester.

(0121)



(0122)

Potassium carbonate 1.0 g (7.04 mmol) and iodomethane 0.6 ml (7.04 mmol) were added to N, N-dimethylformamide (10 ml) solution of 2-amino benzamide benzoic acid ethyl ester 1.0 g (3.52 mmol), and the mixture was stirred at room temperature for 16 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 710 mg (yield 64.6 %) were obtained.

(0123)

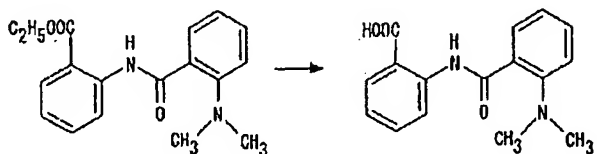
NMR (CDCl₃) delta: 1.39 (3H, t, J = 7 Hz), 2.82 (6H, s), 4.35 (2H, q, J = 7 Hz), 7.06-7.12 (2H, m), 7.15 (1H, dd, J = 8 Hz, 1 Hz), 7.42 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.56 (1H, dd, J = 8 Hz, 1 Hz), 7.96 (1H, dd, J = 8 Hz, 1 Hz), 8.02 (1H, dd, J = 8 Hz, 1 Hz), 8.93 (1H, dd, J = 8 Hz, 1 Hz), 12.60 (1H, s).

(0124)

Example 13

2-(2-dimethylamino benzamide) benzoic acid.

(0125)



(0126)

1N-sodium hydroxide solution 10 ml were added to 2-(2-dimethylamino benzamide) benzoic acid ethyl ester 484 mg (1.55 mmol) ethanol solution (10 ml) produced in Reference Example 8, and the mixture was heated under reflux for two hours. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was

distilled under reduced pressure. The residue was recrystallised using ether / hexane, and title compound 337 mg (yield 76.5 %) were obtained.

(0127)

NMR (CDCl₃) delta: 4.27 (4H, s), 7.09-7.18 (3H, m), 7.44 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.64 (1H, dt, J = 8 Hz, 1 Hz), 7.99 (1H, dd, J = 7 Hz, 1 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.97 (1H, dd, J = 8 Hz, 1 Hz).

IR (v, cm⁻¹, KBr): 3400-2400, 1716, 1636, 1580, 1512, 1450, 1378, 1208, 770, 758.

EI-MS (m/z, %): 284 (M⁺, 15), 270 (3), 148 (100), 147 (88), 105 (16), 91 (24), 77 (19).

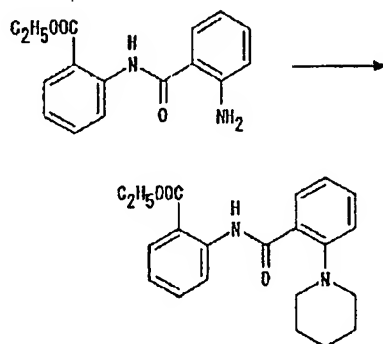
mp: 137-138 degrees.

(0128)

Reference Example 9

2-(2-piperidyl benzamide) benzoic acid ethyl ester.

(0129)



(0130)

Potassium carbonate 510 mg (3.69 mmol) and 1,5-diiodo pentane 0.3 ml (2.11 mmol) were added to N, N-dimethylformamide (15 ml) solution of 2-amino benzamide benzoic acid ethyl ester 500 mg (1.76 mmol), and the mixture was stirred at 60 degC for 20 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed with water, saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 75 mg (yield 12.1 %) were obtained.

(0131)

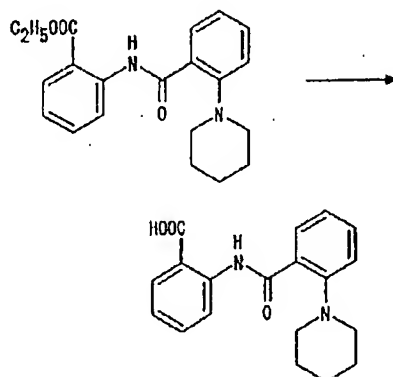
NMR (CDCl₃) delta: 1.36 (3H, t, J = 7 Hz), 1.42-1.50 (2H, m), 1.56-1.67 (4H, m), 3.03 (4H, t, J = 5 Hz), 4.32 (2H, q, J = 7 Hz), 7.05-7.14 (3H, m), 7.41 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.57 (1H, dt, J = 8 Hz, 1 Hz), 7.86 (1H, dd, J = 8 Hz, 1 Hz), 8.06 (1H, dd, J = 8 Hz, 1 Hz), 8.84 (1H, d, J = 8 Hz), 12.29 (1H, s).

(0132)

Example 14

2-(2-piperidyl benzamide) benzoic acid.

(0133)



(0134)

1N-sodium hydroxide solution 10 ml were added to 2-(2-piperidyl benzamide) benzoic acid ethyl ester 75 mg (0.21 mmol) ethanol solution (10 ml) produced in Reference Example 9, and the mixture was heated under reflux for two hours. Ethanol was eliminated by distillation under reduced pressure and the residue was acidified at concentrated hydrochloric acid and was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was distilled under reduced pressure. The residue was recrystallised using ethyl acetate / hexane, and title compound 57 mg (yield 76.5 %) were obtained.

(0135)

NMR (CDCl₃) delta: 1.43-1.50 (2H, m), 1.50-1.65 (4H, m), 2.88-3.08 (4H, m), 7.08-7.20 (3H, m), 7.44 (1H, dt, J = 8 Hz, 1 Hz), 7.61 (1H, dt, J = 8 Hz, 1 Hz), 7.91 (1H, dd, J = 8 Hz, 1 Hz), 8.83 (1H, d, J = 8 Hz).

IR (v, cm⁻¹, KBr): 3400-2100, 1676, 1576, 1520, 1452, 1418, 1270, 908, 766, 756.

EI-MS (m/z, %): 324 (M⁺, 15), 188 (90), 187 (100), 159 (36).

mp: 192-193 degrees.

(0136)

Reference Example 10

2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0137)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (10 ml) of 2-chloro-4-phenyl-ethynyl benzoic acid 0.82 g (3.19 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate 10 ml, and this was dropwise-added under ice cooling to mixed solution of 5 ml of ethyl acetate and 15 ml of water containing potassium carbonate 0.88 g (6.39 mmol) and 2-ethyl aminobenzoic acid 0.47 ml (3.19 mmol) and it was stirred at room temperature for three hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 1.08 g (yield 83.8 %) were obtained.

(0138)

NMR (CDCl₃) delta: 1.40 (3H, t, J = 7 Hz), 4.37 (2H, q, J = 7 Hz), 7.16 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.35-7.41 (3H, m), 7.39-7.58 (3H, m), 7.59-7.66 (3H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.89 (1H, d, J = 8 Hz), 11.62 (1H, s).

(0139)

Reference Example 11

2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid.

(0140)

1M-sodium hydroxide solution 20 ml were added to ethanol (20 ml) solution of benzoic acid ethyl ester 1.03 g (2.55 mmol) produced in Reference Example 10, and it was heated with stirring for one hour, and next ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was added to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with ethanol, and title compound 0.82 g (yield 86.0 %) were obtained.

(0141)

NMR (DMSO-d₆) delta: 7.26 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.45-7.50 (3H, m), 7.59-7.65 (2H, m), 7.66-7.72 (2H, m), 7.77 (1H, d, J = 8 Hz), 7.83 (1H, d, J = 1 Hz), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.57 (1H, d, J = 8 Hz), 11.67 (1H, s).

(0142)

Example 15

2-(2-hexyl amino-4-phenyl-ethynyl benzamide) benzoic acid.

(0143)

Potassium carbonate 140 mg (0.96 mmol) and 5 wt.% activated copper was added to hexylamine (5 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 300 mg (0.80 mmol) produced in Reference Example 10, and it was heated with stirring at 170 degrees in sealed tube for three hours, and next it was cooled to room temperature, and hexylamine was eliminated by distillation under reduced pressure. 1M-hydrochloric acid was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 0.12 g (yield 33.0 %) were obtained.

(0144)

NMR (CDCl₃) delta: 0.91 (3H, t, J = 7 Hz), 1.28-1.40 (4H, m), 1.40-1.50 (2H, m), 1.68-1.76 (2H, m), 3.20 (2H, t, J = 7 Hz), 6.83 (1H, dd, J = 8 Hz, 1 Hz), 6.89 (1H, d, J = 1 Hz), 7.14 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.34-7.39 (3H, m), 7.54-7.60 (2H, m), 7.60-7.69 (2H, m), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.64 (1H, s).

IR (ν , cm⁻¹, KBr): 3344, 2932, 1652, 1604, 1532, 1252, 762, 754.
EI-MS (m/z , %): 440 ($m +$, 100), 422 (19), 369 (29), 304 (34), 232 (96).
mp: 211-213 degrees.

(0145)

Example 16

2-(2-benzylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0146)

Potassium carbonate 0.12 g (0.84 mmol) and 5 wt.% activated copper was added to benzylamine (3 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 260 mg (0.70 mmol) produced in Reference Example 10, and it was heated with stirring at 170 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 90 mg (yield 28.7 %) were obtained.

(0147)

NMR (CDCl₃) δ : 4.74 (2H, s), 6.85-6.90 (2H, m), 7.12-7.17 (1H, m), 7.26-7.30 (1H, m), 7.32-7.42 (6H, m), 7.50-7.55 (2H, m), 7.64 (1H, ddd, $J = 8$ Hz, 7 Hz, 1 Hz), 7.71 (1H, d, $J = 8$ Hz), 8.16 (1H, dd, $J = 8$ Hz, 1 Hz), 8.79 (1H, dd, $J = 8$ Hz, 1 Hz), 11.71 (1H, s).
IR (ν , cm⁻¹, KBr): 3240, 1682, 1650, 1604, 1538, 1266, 766, 756.
EI-MS (m/z , %): 446 ($m +$, 100), 428 (37), 310 (84), 280 (87), 221 (42), 193 (69), 91 (22).
mp: 226-228 degrees.

(0148)

Reference Example 12

2-(2-methylpropyl) aminobenzoic acid.

(0149)

Potassium carbonate 1.06 g (7.16 mmol) and 5 wt.% activated copper was added to 2-methylpropyl amine (3 ml) solution of 2-chlorobenzoic acid 1.0 g (6.39 mmol), and it was heated with stirring at 170 degrees in sealed tube for one hour and next was cooled to room temperature. 1M-hydrochloric

acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.99 g (yield 88.0 %) were obtained.

(0150)

NMR (CDCl₃) delta: 1.03 (6H, d, J = 7 Hz), 1.99 (1H, sept, J = 7 Hz), 3.04 (2H, d, J = 7 Hz), 6.56 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.68 (1H, dd, J = 8 Hz, 1 Hz), 7.38 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.98 (1H, dd, J = 8 Hz, 1 Hz).

(0151)

Example 17

2-(2-(2-methylpropyl amino) benzamide) benzoic acid.

(0152)

Thionyl chloride 0.5 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (5 ml) of 2-(2-methylpropyl) aminobenzoic acid 0.30 g (1.55 mmol) produced in Reference Example 12 and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in methylene chloride 10 ml, and under a nitrogen atmosphere, to triethylamine 0.64 ml (4.66 mmol) and methylene chloride (10 ml) solution of 2-aminobenzoic acid 0.21 g (1.55 mmol), it was dropwise-added under ice cooling, and this was stirred at room temperature for 18 hours. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 0.23 g (yield 46.9 %) were obtained.

(0153)

NMR (CDCl₃) delta: 1.06 (6H, d, J = 7 Hz), 2.02 (1H, sept, J = 7 Hz), 3.05 (2H, d, J = 7 Hz), 6.69 (1H, dt, J = 8 Hz, 1 Hz), 6.76 (1H, d, J = 8 Hz), 7.16 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.38 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.67 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.72 (1H, dd, J = 8 Hz, 1 Hz), 8.19 (1H, dd, J = 8 Hz, 1 Hz), 8.84 (1H, dd, J = 8 Hz, 1 Hz), 11.57 (1H, s).
IR (ν, cm⁻¹, KBr): 2962, 1658, 1602, 1576, 1532, 1256, 752, 738.

EI-MS (m/z, %): 312 (m +, 41), 269 (61), 251 (16), 132 (100), 120 (30).
mp: 159-160 degrees.

(0154)

Reference Example 13

2-cyclohexyl aminobenzoic acid.

(0155)

Potassium carbonate 1.06 g (7.16 mmol) and 5 wt.% activated copper was added to cyclohexylamine (3 ml) solution of 2-chlorobenzoic acid 1.0 g (6.39 mmol), and it was heated with stirring at 170 degrees in sealed tube for 30 minutes and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 1.27 g (yield 90.6 %) were obtained.

(0156)

NMR (CDCl₃) delta: 1.34-1.47 (5H, m), 1.60-1.68 (1H, m), 1.74-1.83 (2H, m), 1.98-2.10 (2H, m), 3.36-3.46 (1H, m), 6.56 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 6.71 (1H, d, J = 8 Hz), 7.36 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.96 (1H, dd, J = 8 Hz, 1 Hz).

(0157)

Example 18

2-(2-(cyclohexyl amino) benzamide) benzoic acid.

(0158)

Thionyl chloride 0.5 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (10 ml) of 2-cyclohexyl aminobenzoic acid 0.30 g (1.55 mmol) produced in Reference Example 13 and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in methylene chloride 10 ml, and this was dropwise-added under ice cooling under a nitrogen atmosphere to triethylamine 0.57 ml (4.11 mmol) and methylene chloride (10 ml) solution of 2-aminobenzoic acid 0.19 g (1.37 mmol), and it was stirred at room temperature for 18 hours. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was

washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 0.30 g (yield 59.3 %) were obtained.

(0159)

NMR (CDCl₃) delta: 1.26-1.40 (3H, m), 1.40-1.52 (2H, m), 1.58-1.68 (1H, m), 1.72-1.84 (2H, m), 1.99-2.05 (2H, m), 3.44-3.54 (1H, m), 6.63 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.85 (1H, d, J = 8 Hz), 7.19 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.34 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.67 (1H, dd, J = 8 Hz, 1 Hz), 7.74 (1H, dd, J = 8 Hz, 1 Hz), 8.86 (1H, dd, J = 8 Hz, 1 Hz), 12.07 (1H, s).

IR (ν, cm⁻¹, KBr): 2936, 1658, 1574, 1532, 1252, 754, 740.

EI-MS (m/z, %): 338 (m +, 100), 326 (5), 295 (22), 202 (18), 201 (16), 158 (41), 132 (19), 120 (19).

mp: 230-232 degrees.

(0160)

Reference Example 14

2-(2-chlorobenzamide) benzoic acid ethyl ester.

(0161)

Thionyl chloride 2.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (30 ml) of 2-chlorobenzoic acid 3.0 g (19.2 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of 15 ml of ethyl acetate and 30 ml of water containing potassium carbonate 5.3 g (38.3 mmol) and 2-ethyl aminobenzoic acid 2.8 ml (19.2 mmol) and it was stirred at room temperature for three hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ether-hexane, and title compound 5.2 g (yield 89.7 %) were obtained.

(0162)

NMR (CDCl₃) delta: 1.39 (3H, t, J = 7 Hz), 4.36 (2H, J = 7 Hz), 7.16 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.34-7.43 (2H, m), 7.45-7.49 (1H, m), 7.61 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.66 (1H, dd, J = 8 Hz, 1 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.90 (1H, d, J = 8 Hz) 11.55 (1H, s).

(0163)

Reference Example 15

2-(2-chlorobenzamide) benzoic acid.

(0164)

1M-sodium hydroxide solution 50 ml were added to ethanol (50 ml) solution of (2-chlorobenzamide) benzoic acid ethyl ester 5.22 g (17.2 mmol) and were heated under reflux for three hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 4.15 g (yield 87.6 %) were obtained.

(0165)

NMR (DMSO-d₆) delta: 7.22 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.49 (1H, ddd, J = 7.7 Hz, 1 Hz), 7.55 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.58-7.68 (2H, m), 7.70 (1H, dd, J = 7.1 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.60 (1H, d, J = 8 Hz), 11.95 (1H, s).

(0166)

Example 19

2-(2-hexyl amino benzamide) benzoic acid.

(0167)

Potassium carbonate 240 mg (1.74 mmol) and 5 wt.% activated copper was added to hexylamine (6 ml) solution of 2-(2-chlorobenzamide) benzoic acid 400 mg (1.45 mmol) produced in Reference Example 15 and it was heated with stirring at 170 degrees in sealed tube for one hour 30 minutes and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 370 mg (yield 75.8 %) were obtained.

(0168)

NMR (CDCl₃) delta: 0.90 (3H, t, J = 7 Hz), 1.28-1.50 (6H, m), 1.64-1.74 (2H, m), 3.19 (2H, t, J = 7 Hz), 6.67 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.74 (1H, d, J = 8 Hz), 7.14 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.36 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.64 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.68 (1H, dd, J = 8 Hz, 1 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.52 (1H, s).

IR (ν, cm⁻¹, KBr): 2924, 2856, 1698, 1646, 1612, 1574, 1538, 1294, 1222, 756, 740.

EI-MS (m/z, %): 340 (m+, 94), 322 (13), 269 (75), 251 (26), 204 (32), 132 (100), 120 (30).

mp: 151-152 degrees.

(0169)

Example 20

2-(2-(2,2-dimethylpropyl amino) benzamide) benzoic acid.

(0170)

Potassium carbonate 240 mg (1.74 mmol) and 5 wt.% activated copper was added to 2,2-dimethylpropyl amine (7 ml) solution of 2-(2-chlorobenzamide) benzoic acid 400 mg (1.45 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees in sealed tube for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ether-hexane, and title compound 170 mg (yield 36.3 %) were obtained.

(0171)

NMR (CDCl₃) delta: 1.06 (9H, m), 2.99 (2H, s), 6.64 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.13 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.34 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.65 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.70 (1H, dd, J = 8 Hz, 1 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.83 (1H, dd, J = 8 Hz, 1 Hz), 11.57 (1H, s).

IR (ν, cm⁻¹, KBr): 3368, 2960, 1666, 1578, 1526, 1262, 758, 746.

EI-MS (m/z, %): 326 (m+, 47), 269 (89), 251 (22), 132 (100), 120 (23).

mp: 193-194 degrees.

(0172)

Example 21

2-(2-octyl amino benzamide) benzoic acid.

(0173)

Potassium carbonate 0.24 g (1.74 mmol) and 5 wt.% activated copper was added to octyl amine (4 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.40 g (1.45 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with ethanol, and title compound 0.25 g (yield 45.9 %) were obtained.

(0174)

NMR (CDCl₃) delta: 0.89 (3H, t, J = 7 Hz), 1.24-1.39 (8H, m), 1.39-1.49 (2H, m), 1.65-1.75 (2H, m), 3.19 (2H, t, J = 7 Hz), 6.67 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.75 (1H, d, J = 8 Hz), 7.14 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.36 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.64 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.69 (1H, dd, J = 8 Hz, 1 Hz), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.67 (1H, s).

IR (v, cm⁻¹, KBr): 3228, 2928, 2852, 1698, 1646, 1610, 1574, 1540, 1292, 1204, 756, 738.

EI-MS (m/z, %): 368 (m⁺, 90), 340 (25), 269 (96), 251 (22), 132 (100), 120 (30).

mp: 146-147 degrees.

(0175)

Example 22

2-(2-decyl amino benzamide) benzoic acid.

(0176)

Potassium carbonate 240 mg (1.74 mmol) and 5 wt.% activated copper was added to decyl amine (4 ml) solution of 2-(2-chlorobenzamide) benzoic acid 400 mg (1.45 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by

silica gel chromatography, and thereafter, it was recrystallised with acetonitrile, and title compound 300 mg (yield 51.9 %) were obtained.

(0177)

NMR (CDCl₃) delta: 0.88 (3H, t, J = 7 Hz), 1.20-1.38 (12H, m), 1.38-1.48 (2H, m), 1.65-1.74 (2H, m), 3.18 (2H, t, J = 7 Hz), 6.66 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 6.75 (1H, d, J = 8 Hz), 7.13 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.35 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.64 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.69 (1H, dd, J = 8 Hz, 1 Hz), 8.15 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.58 (1H, s).

IR (ν, cm⁻¹, KBr): 3326, 2924, 2852, 1698, 1646, 1610, 1574, 1540, 1294, 1200, 756, 736.

EI-MS (m/z, %): 396 (m +, 74), 368 (28), 340(11), 269 (100), 251 (26), 132 (78), 120 (30).

mp: 126-127 degrees.

(0178)

Reference Example 16

2-(2-iso indolyl benzamide) benzoic acid ethyl ester.

(0179)

Potassium carbonate 530 mg (3.87 mmol) and alpha, alpha'-dibromo-o-xylene 470 mg (1.76 mmol) were added to N, N-dimethylformamide (5 ml) solution of 2-(2-amino benzamide) benzoic acid ethyl ester 500 mg (1.76 mmol), and it was heated with stirring at 110 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid solution was added to the reaction solution and was extracted with acetic acid ethyl ester. The organic layer was washed with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 360 mg (yield 53.1 %) were obtained.

(0180)

NMR (CDCl₃) delta: 1.31 (3H, t, J = 7 Hz), 4.22 (2H, q, J = 7 Hz), 4.75 (4H, m), 6.88 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 6.97 (1H, d, J = 8 Hz), 7.13 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.58-7.65 (2H, m), 8.05 (1H, dd, J = 8 Hz, 1 Hz), 8.95 (1H, d, J = 8 Hz), 11.66 (1H, s).

(0181)

Example 23

2-(2-iso indolyl benzamide) benzoic acid.

(0182)

1M-sodium hydroxide solution (5 ml) was added to ethanol (5 ml) solution of 2-(2-iso indolyl benzamide) benzoic acid ethyl ester 360 mg (0.93 mmol) produced in Reference Example 16 and was heated under reflux for two hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. To the residue, concentrated hydrochloric acid was dropwise-added under ice cooling, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 260 mg (yield 77.7 %) were obtained.

(0183)

NMR (CDCl₃) delta: 4.71 (4H, s), 6.90 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 6.99 (1H, d, J = 8 Hz), 7.13-7.23 (5H, m), 7.40 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.63 (1H, dd, J = 7.1 Hz), 7.67 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 8.08 (1H, dd, J = 8 Hz, 1 Hz), 8.97 (1H, d, J = 8 Hz), 11.48 (1H, s).

IR (ν, cm⁻¹, KBr): 3328, 1668, 1518, 1264, 756.

EI-MS (m/z, %): 358 (m +, 15), 312 (7), 269 (10), 221 (52), 193 (100), 132 (14).

mp: 185-186 degrees.

(0184)

Example 24

2-(2-(1-propyl butyl) amino benzamide) benzoic acid.

(0185)

Potassium carbonate 0.15 g (1.11 mmol) and 5 wt.% activated copper was added to 4-heptyl amine (3 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.26 g (0.93 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees in sealed tube for five hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.15 g (yield 45.0 %) were obtained.

(0186)

NMR (CDCl₃) delta: 0.92 (6H, t, J = 7 Hz), 1.30-1.62 (8H, m), 3.50 (1H, pent, J = 6 Hz), 6.61 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 6.75 (1H, d, J = 8 Hz), 7.13 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.32 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.68 (1H, dd, J = 8 Hz, 1 Hz), 8.79 (1H, dd, J = 8 Hz, 1 Hz), 11.55 (1H, s).

IR (ν, cm⁻¹, KBr): 2956, 2928, 1652, 1602, 1578, 1532, 1256, 752, 742.

EI-MS (m/z, %): 354 (m +, 22), 311 (75), 293 (6), 174 (100), 146 (19), 132 (13).

mp: 139-140 degrees.

(0187)

Example 25

2-(2-(1-methyl hexyl) amino benzamide) benzoic acid

(0188)

Potassium carbonate 0.21 g (1.52 mmol) and 5 wt.% activated copper was added to 2-amino heptane (3 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.35 g (1.27 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees in sealed tube for five hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from hexane, and title compound 0.23 g (yield 50.4 %) were obtained.

(0189)

NMR (CDCl₃) delta: 0.88 (3H, t, J = 7 Hz), 1.24 (3H, d, J = 6 Hz), 1.26-1.56 (7H, m), 1.58-1.70 (1H, m), 3.56 (1H, q, J = 6 Hz), 6.63 (1H, dd, J = 7 Hz, 7 Hz), 6.74 (1H, d, J = 8 Hz), 7.10-7.16 (1H, m), 7.30-7.38 (1H, m), 7.60-7.66 (1H, m), 7.69 (1H, dd, J = 8 Hz, 1 Hz), 8.15 (1H, dd, J = 8 Hz, 1 Hz), 8.79 (1H, d, J = 8 Hz), 11.54 (1H, s).

IR (ν, cm⁻¹, KBr): 2952, 2932, 1698, 1652, 1612, 1574, 1538, 1264, 756, 742.

EI-MS (m/z, %): 354 (m +, 22), 336 (4), 311 (28), 283 (67), 174 (100), 146 (19), 132 (13).

mp: 108-109 degrees.

(0190)

Example 26

2-(2-(2-ethylhexyl) amino benzamide) benzoic acid.

(0191)



(0192)

Potassium carbonate 0.24 g (1.74 mmol) and 5 wt.% activated copper was added to 2-ethylhexyl amine (3 ml) solution of 2-(2-chlorobenzamido) benzoic acid 0.40 g (1.45 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees in sealed tube for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.25 g (yield 47.4 %) were obtained.

(0193)

NMR (CDCl₃) delta: 0.86-0.96 (6H, m), 1.26-1.54 (8H, m), 1.61-1.72 (1H, m), 3.09 (1H, dd, J = 12 Hz, 6 Hz), 3.11 (1H, dd, J = 12 Hz, 6 Hz), 6.63-6.68 (1H, m), 6.74 (1H, d, J = 8 Hz), 7.13 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.36 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.64 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.69 (1H, dd, J = 7.1 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.82 (1H, dd, J = 8 Hz, 1 Hz), 11.55 (1H, s).

IR (ν, cm⁻¹, KBr): 2960, 2924, 1654, 1602, 1530, 1256, 788, 746.

EI-MS (m/z, %): 368 (m +, 23), 269 (70), 251 (18), 174 (3), 146 (5), 132 (100), 120 (28).

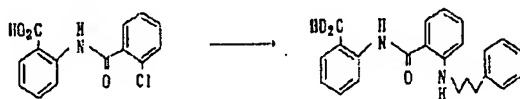
mp: 120-121 degrees.

(0194)

Example 27

2-(2-(3-phenylpropyl) amino benzamide) benzoic acid.

(0195)



(0196)

Potassium carbonate 0.18 g (1.31 mmol) and 5 wt.% activated copper was added to 3-phenyl propylamine (3 ml) solution of 2-(2-chlorobenzamide) benzoic acid 0.30 g (1.09 mmol) produced in Reference Example 15, and it was heated with stirring at 170 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.18 g (yield 42.9 %) were obtained.

(0197)

NMR (CDCl₃) delta: 1.98-2.08 (2H, m), 2.77 (2H, t, J = 7 Hz), 3.21 (2H, t, J = 7 Hz), 6.64-6.72 (2H, m), 7.10-7.24 (4H, m), 7.24-7.36 (3H, m), 7.61-7.67 (1H, m), 7.70 (1H, dd, J = 8 Hz, 1 Hz), 8.15 (1H, dd, J = 8 Hz, 1 Hz), 8.82 (1H, d, J = 8 Hz), 11.61 (1H, s).

IR (ν, cm⁻¹, KBr): 2920, 1650, 1602, 1574, 1534, 1262, 758.

EI-MS (m/z, %): 374 (m +, 51), 356 (3), 269 (69), 251 (22), 174 (5), 146 (14), 132 (100), 120 (36).

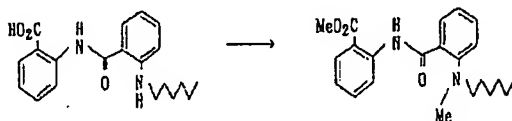
mp: 202-203 degrees.

(0198)

Reference Example 17

2-(2-(N-methyl hexyl amino) benzamide) methyl benzoate ester.

(0199)



(0200)

Potassium carbonate 0.13 g (0.97 mmol) and iodo methane 0.1 ml (1.76 mmol) were added to N, N-dimethylformamide (5 ml) solution of 2-(2-hexyl amino benzamide) benzoic acid 0.15 g (0.44 mmol) produced in Example 19, and the mixture was stirred at 50 degrees for 17 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.14 g (yield 85.7 %) were obtained.

(0201)

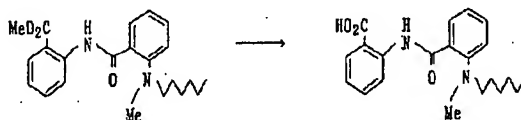
NMR (CDCl₃) delta: 0.78 (3H, t, J = 7 Hz), 1.10-1.22 (6H, m), 1.40-1.50 (2H, m), 2.83 (3H, s), 2.97-3.04 (2H, m), 3.88 (3H, s), 7.07-7.14 (2H, m), 7.17 (1H, d, J = 8 Hz), 7.41 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.54-7.60 (1H, m), 7.98 (2H, ddd, J = 9.8, 1 Hz), 8.86 (1H, d, J = 8 Hz), 12.58 (1H, s).

(0202)

Example 28

2-(2-(N-methyl hexyl amino) benzamide) benzoic acid.

(0203)



(0204)

1M-sodium hydroxide solution 5 ml were added to ethanol (5 ml) solution of 2-(2-(N-methyl hexyl amino) benzamide) methyl benzoate 0.14 g (0.38 mmol) produced in Reference Example 17 and were heated under reflux for two hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 0.09 g (yield 68.1 %) were obtained.

(0205)

NMR (CDCl₃) delta: 0.71-0.77 (3H, m), 1.05-1.15 (6H, m), 1.38-1.50 (2H, m), 2.78 (3H, s), 2.92-3.00 (2H, m), 7.08-7.18 (3H, m), 7.38-7.66 (1H, m), 7.98 (1H, dd, J = 8 Hz, 1 Hz), 8.08 (1H, dd, J = J = 8 Hz, 1 Hz), 8.87 (1H, d, J = 8 Hz).

IR (ν, cm⁻¹, KBr): 2928, 1664, 1586, 1516, 1234, 756.

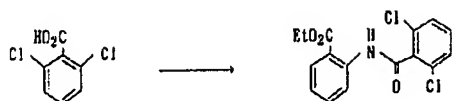
EI-MS (m/z, %): 354 (m +, 22), 283 (42), 265 (46), 218 (69), 217 (93), 146 (46), 134 (100), 132 (67).

(0206)

Reference Example 18

2-(2,6-dichlorobenzamide) benzoic acid ethyl ester.

(0207)



(0208)

Thionyl chloride 2.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (20 ml) of 2,6-dichloro benzoic acid 3.0 g (15.7 mmol) and were heated under reflux for two hours, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of 20 ml of ethyl acetate and 30 ml of water containing potassium carbonate 4.3 g (31.4 mmol) and 2-ethyl aminobenzoic acid 2.3 ml (15.7 mmol) and it was stirred at room temperature for 42 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 2.8 g (yield 53.6 %) were obtained.

(0209)

NMR (CDCl₃) delta: 1.39 (3H, t, J = 7 Hz), 4.34 (2H, J = 7 Hz), 7.16-7.22 (1H, m), 7.30 (1H, dd, J = 9 Hz, 2 Hz), 7.61-7.67 (1H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.90 (1H, dd, J = 8 Hz, 1 Hz), 11.39 (1H, s).

(0210)

Reference Example 19

2-(2,6-dichlorobenzamide) benzoic acid.

(0211)



(0212)

1M-sodium hydroxide solution (20 ml) was added to ethanol (20 ml) solution of benzoic acid ethyl ester 2.82 g (8.34 mmol) produced in Reference Example 18, and it was heated under reflux for 6 hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 2.08 g (yield 80.3 %) were obtained.

(0213)

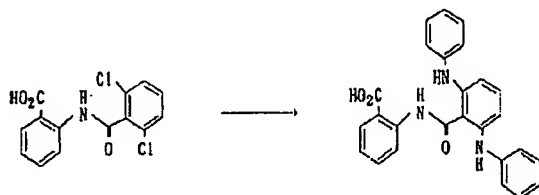
NMR (DMSO-d₆) delta: 7.28 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.55 (1H, dd, J = 9 Hz, 7 Hz), 7.60-7.65 (2H, m), 7.70 (1H, ddd, J = 9 Hz, 8 Hz, 1 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.55 (1H, dd, J = 8 Hz, 1 Hz), 11.56 (1H, s).

(0214)

Example 29

2-(2,6-diphenylamino benzamide) benzoic acid.

(0215)



(0216)

Potassium carbonate 0.32 g (2.32 mmol) and 5 wt.% activated copper was added to aniline (3 ml) solution of 2-(2,6-dichlorobenzamide) benzoic acid 0.30 g (0.97 mmol) produced in Reference Example 19 and was heated under reflux for four hours and thereafter, was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel

chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.13 g (yield 30.8 %) were obtained.

(0217)

NMR (CDCl₃) delta: 6.83 (2H, d, J = 8 Hz), 6.89-6.95 (2H, m), 7.06-7.16 (6H, m), 7.20-7.28 (4H, m), 7.53-7.59 (1H, m), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.72 (1H, d, J = 8 Hz), 11.53 (1H, s).

IR (v, cm⁻¹, KBr): 2960, 1680, 1658, 1574, 1508, 1262, 752.

EI-MS (m/z, %): 439 (m +, 57), 421 (10), 368 (8), 303 (23), 302 (22), 276 (73), 231 (52), 205 (100).

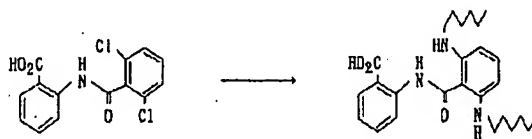
mp: 110-111 degrees.

(0218)

Example 30

2-(2,6-dihexyl amino benzamide) benzoic acid.

(0219)



(0220)

Potassium carbonate 0.32 g (2.32 mmol) and 5 wt.% activated copper was added to hexylamine (3 ml) solution of 2-(2,6-dichlorobenzamide) benzoic acid 0.30 g (0.97 mmol) produced in Reference Example 19, and it was heated with stirring at 170 degrees in sealed tube for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ether-hexane, and title compound 0.21 g (yield 49.9 %) were obtained.

(0221)

NMR (CDCl₃) delta: 0.82 (3H, t, J = 7 Hz), 1.19-1.39 (6H, m), 1.56-1.62 (2H, m), 3.08 (2H, t, J = 7 Hz), 6.10 (2H, d, J = 8 Hz), 7.09-7.17 (2H, m), 7.62 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, d, J = 8 Hz).

IR (ν , cm⁻¹, KBr): 1682, 1646, 1580, 1520, 1270, 748.

EI-MS (m/z , %): 423 (m +, 27), 405 (13), 368 (100), 286 (42), 236 (45).

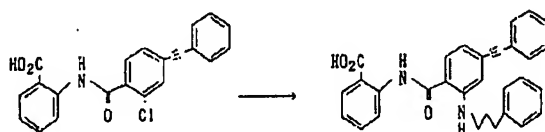
mp: 195-197 degrees.

(0222)

Example 31

2-(4-phenyl-ethynyl-2-(3-phenylpropyl amino) benzamide) benzoic acid.

(0223)



(0224)

Potassium carbonate 0.18 g (1.28 mmol) and 5 wt.% activated copper was added to 3-phenyl propylamine (3 ml) solution of 2-(2-chloro-4-phenylethynyl benzamide) benzoic acid 0.40 g (1.06 mmol) produced in Reference Example 10, and it was heated with stirring at 180 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised with methanol, and title compound 0.30 g (yield 59.2 %) were obtained.

(0225)

NMR (CDCl₃) δ : 2.06 (2H, pent, J = 7 Hz), 2.78 (2H, t, J = 7 Hz), 3.23 (2H, t, J = 7 Hz), 6.82-6.87 (2H, m), 7.13-7.32 (7H, m), 7.34-7.39 (3H, m), 7.54-7.58 (2H, m), 7.62-7.69 (2H, m), 8.18 (1H, dd, J = 8 Hz, 1 Hz), 8.81 (1H, d, J = 8 Hz), 11.62 (1H, s).

IR (ν , cm⁻¹, KBr): 2936, 1650, 1604, 1586, 1538, 1260, 754.

EI-MS (m/z , %): 474 (m +, 80), 456 (57), 374 (20), 351 (50), 269 (23), 232 (100), 176 (27), 132 (41), 120 (22), 91 (72).

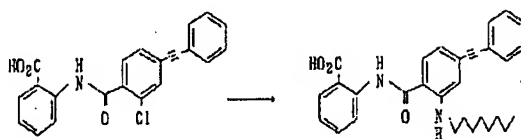
mp: 199-200 degrees.

(0226)

Example 32

2-(2-octyl amino-4-phenyl-ethynyl benzamide) benzoic acid.

(0227)



(0228)

Potassium carbonate 0.18 g (1.28 mmol) and 5 wt.% activated copper was added to octyl amine (3 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 0.40 g (1.06 mmol) produced in Reference Example 10, and it was heated with stirring at 180 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.05 g (yield 9.6 %) were obtained.

(0229)

NMR (CDCl₃) delta: 0.88 (3H, t, J = 7 Hz), 1.22-1.40 (8H, m), 1.40-1.50 (2H, m), 1.78 (2H, pent, J = 7 Hz), 3.20 (2H, t, J = 7 Hz), 6.83 (1H, dd, J = 8 Hz, 1 Hz), 6.89 (1H, d, J = 1 Hz), 7.12-7.18 (1H, m), 7.34-7.40 (3H, m), 7.56-7.60 (2H, m), 7.63-7.69 (2H, m), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.59 (1H, s).

IR (ν, cm⁻¹, KBr): 2924, 1656, 1604, 1564, 1520, 1254, 752.

EI-MS (m/z, %): 450 (M-H₈, 49), 421 (10), 368 (18), 351 (72), 176 (15).

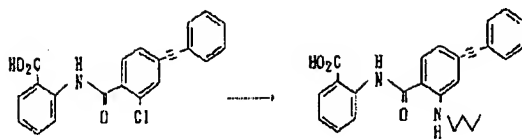
mp: 162-163 degrees.

(0230)

Example 33

2-(2-butylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0231)



(0232)

Potassium carbonate 0.13 g (0.96 mmol) and 5 wt.% activated copper was added to butyl amine (2 ml) solution of 2-(2-chloro-4-phenylethynyl benzamide) benzoic acid 0.30 g (0.80 mmol) produced in Reference Example 10, and it was heated with stirring at 180 degrees in sealed tube for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 018 g (yield 53.2 %) were obtained.

(0233)

NMR (CDCl₃) delta: 0.98 (3H, t, J = 7 Hz), 1.44-1.54 (2H, m), 1.66-1.76 (2H, m), 3.02 (2H, t, J = 7 Hz), 6.83 (1H, dd, J = 8 Hz, 1 Hz), 6.89 (1H, d, J = 1 Hz), 7.12-7.18 (1H, m), 7.33-7.40 (3H, m), 7.54-7.60 (2H, m), 7.62-7.68 (2H, m), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.59 (1H, s).

IR (ν, cm⁻¹, KBr): 3438, 2956, 1680, 1650, 1540, 1262, 754.

EI-MS (m/z, %): 412 (m +, 69), 394 (12), 369 (22), 276 (33), 232 (100), 176 (23).

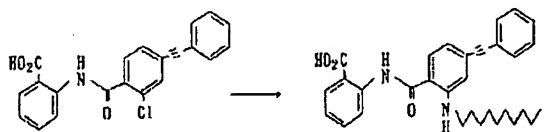
mp: 217-219 degrees.

(0234)

Example 34

2-(3-decyl amino-4-phenylethynyl benzamide) benzoic acid.

(0235)



(0236)

Potassium carbonate 0.13 g (0.96 mmol) and 5 wt.% activated copper was added to decyl amine (3 ml) solution of 2-(2-chloro-4-phenyl-ethynyl benzamide) benzoic acid 0.30 g (0.80 mmol) produced in Reference Example 10, and it was heated with stirring at 180 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.08 g (yield 18.9 %) were obtained.

(0237)

NMR (CDCl₃) delta: 0.87 (3H, t, J = 7 Hz), 1.20-1.40 (12H, m), 1.40-1.50 (2H, m), 1.66-1.76 (2H, m), 3.20 (2H, t, J = 7 Hz), 6.83 (1H, dd, J = 8 Hz, 1 Hz), 6.89 (1H, d, J = 1), 7.12-7.18 (1H, m), 7.23-7.40 (3H, m), 7.53-7.59 (2H, m), 7.62-7.68 (2H, m), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.60 (1H, s).

IR (ν, cm⁻¹, KBr): 2924, 1652, 1608, 1538, 1258, 764, 754.

EI-MS (m/z, %): 496 (m +, 42), 478 (87), 369 (26), 351 (100), 323 (30), 232 (45).

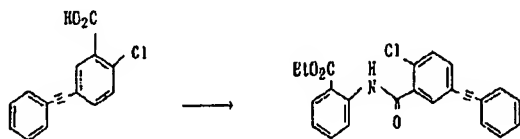
mp: 144-146 degrees.

(0238)

Reference Example 20

2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0239)



(0240)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (15 ml) of 2-chloro-5-phenyl-ethynyl benzoic acid 2.0 g (7.79 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of 10 ml of ethyl acetate and 15 ml of water containing

potassium carbonate 2.1 g (15.6 mmol) and ethyl aminobenzoic acid 1.1 ml (7.79 mmol) and it was stirred at room temperature for two hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 1.7 g (yield 53.4 %) were obtained.

(0241)

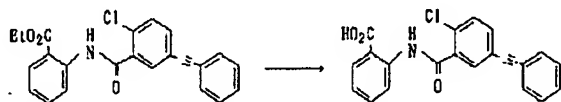
NMR (CDCl₃) delta: 1.40 (3H, t, J = 7 Hz), 4.37 (2H, q, J = 7 Hz), 7.14-7.20 (1H, m), 7.33-7.38 (3H, m), 7.45 (1H, d, J = 8 Hz), 7.50-7.56 (3H, m), 7.60-7.66 (1H, m), 7.80 (1H, d, J = 2 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.88 (1H, d, J = 8 Hz), 11.57 (1H, s).

(0242)

Reference Example 21

2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid.

(0243)



(0244)

1M-sodium hydroxide solution 20 ml were added to ethanol (15 ml) solution of 2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 1.68 g (4.16 mmol) produced in Reference Example 20 and were heated under reflux for two hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 1.53 g (yield 97.8 %) were obtained.

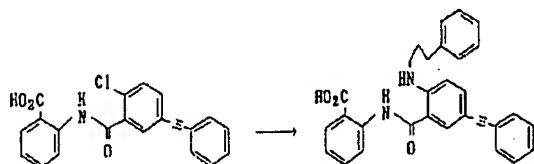
NMR (DMSO-d₆) delta: 7.24-7.30 (1H, m), 7.43-7.48 (3H, m), 7.57-7.63 (2H, m), 7.65-7.74 (3H, m), 7.91 (1H, d, J = 2 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.50 (1H, d, J = 8 Hz), 11.61 (1H, s), 13.71 (1H, br-s).

(0245)

Example 35

2-(5-phenyl-ethynyl-2-(3-phenylpropyl) amino benzamide) benzoic acid.

(0246)



(0247)

Potassium carbonate 0.13 g (0.96 mmol) and 5 wt.% activated copper was added to 3-phenyl propylamine (1.5 ml) solution of 2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid 0.30 g (0.80 mmol) produced in Reference Example 21, and it was heated with stirring at 180 degrees for three hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.15 g (yield 38.6 %) were obtained.

(0248)

NMR (CDCl₃) delta: 2.00-2.09 (2H, m), 2.78 (2H, t, J = 7 Hz), 3.24 (2H, t, J = 7 Hz), 6.65 (1H, d, J = 8 Hz), 6.95-7.02 (1H, m), 7.17-7.33 (8H, m), 7.46-7.55 (3H, m), 7.58-7.64 (1H, m), 7.91 (1H, d, J = 2 Hz), 8.01 (1H, d, J = 8 Hz), 8.79 (1H, d, J = 8 Hz), 11.70 (1H, s).

IR (ν, cm⁻¹, KBr): 2928, 1658, 1604, 1532, 1262, 756.

El-MS (m/z, %): 474 (m +, 9), 456 (100), 383 (36), 351 (46), 232 (9).

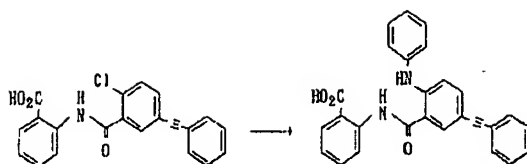
mp: 194-196 degrees.

(0249)

Example 36

2-(2-phenylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0250)



(0251)

Potassium carbonate 0.13 g (0.96 mmol) and 5 wt.% activated copper was added to 3-phenyl propylamine (1.5 ml) solution of 2-(2-chloro-5-phenylethynyl benzamide) benzoic acid 0.30 g (0.80 mmol) produced in Reference Example 21, and it was heated with stirring at 180 degrees for one hour 30 minutes and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, it was recrystallised from ethyl acetate-hexane, and title compound 0.17 g (yield 50.7 %) were obtained.

(0252)

NMR (CDCl₃) delta: 6.99-7.04 (1H, m), 7.07-7.12 (1H, m), 7.22-7.39 (8H, m), 7.46 (1H, dd, J = 8 Hz, 2 Hz), 7.50-7.56 (2H, m), 7.61-7.66 (1H, m), 7.97 (1H, d, J = 2 Hz), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.81 (1H, d, J = 8 Hz), 9.81 (1H, s), 11.79 (1H, s).

IR (ν, cm⁻¹, KBr): 1682, 1646, 1580, 1520, 1270, 748.

EI-MS (m/z, %): 423 (m +, 27), 405 (13), 368 (100), 286 (42), 236 (45).

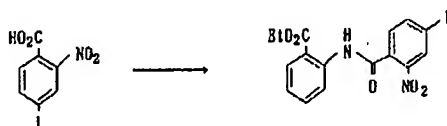
mp: 199-202 degrees.

(0253)

Reference Example 22

2-(4-iodo-2-nitrobenzamide) benzoic acid ethyl ester.

(0254)



(0255)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (10 ml) of 4-iodo-2-nitrobenzoic acid 1.82 g (6.21 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (15 ml) and this was dropwise-added under ice cooling to mixed solution of 5 ml of ethyl acetate and 15 ml of water containing potassium carbonate 1.8 g (13.05 mmol) and 2-ethyl aminobenzoic acid 0.97 ml (6.52 mmol) and it was stirred at room temperature for 16 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 2.25 g (yield 82.3 %) were obtained.

(0256)

NMR (CDCl₃) delta: 1.40 (3H, t, J = 7 Hz), 4.35 (2H, J = 7 Hz), 7.16-7.21 (1H, m), 7.44 (1H, d, J = 8 Hz), 7.59-7.65 (1H, m), 8.05-8.12 (2H, m), 8.39 (1H, d, J = 1 Hz), 8.77 (1H, d, J = 8 Hz), 11.66 (1H, s).

(0257)

Reference Example 23

2-(2-amino-4-iodo benzamide) benzoic acid ethyl ester.

(0258)



(0259)

20 % ammonium sulphide solution 10 ml were dropwise-added to ethanol (10 ml) solution of 2-(4-iodo-2-nitrobenzamide) benzoic acid ethyl ester 2.25 g (5.11 mmol) produced in Reference Example 22 and were heated under reflux for four hours. The reaction solution was cooled with ice, and unnecessary matter was filtered. 4M hydrochloric acid was added to filtrate, and it was acidified, and next extraction was carried out with ethyl acetate. The organic layer was washed successively at water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from methylene chloride, and title compound 0.97 g (yield 46.5 %) were obtained.

(0260)

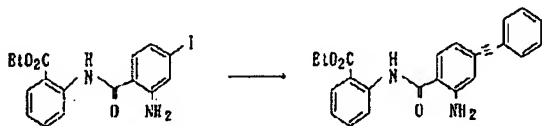
NMR (CDCl₃) delta: 1.42 (3H, t, J = 7 Hz), 4.41 (2H, J = 7 Hz), 7.07-7.14 (3H, m), 7.41 (1H, d, J = 8 Hz), 7.58 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.77 (1H, J = 8 Hz, 1 Hz), 11.88 (1H, s).

(0261)

Reference Example 24

2-(2-amino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0262)



(0263)

Under a nitrogen atmosphere, phenyl acetylene 0.4 ml (3.55 mmol), dichlorobis triphenylphosphine palladium 0.02 g (0.02 mmol) and copper iodide 0.01 g (0.04 mmol) were added to diethylamine (10 ml) solution of 2-(2-amino-4-iodo benzamide) benzoic acid ethyl ester 0.97 g (2.36 mmol) produced in Reference Example 23, and the mixture was stirred at room temperature for one hour, and next diethylamine was eliminated by distillation under reduced pressure. 1M-hydrochloric acid was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from chloroform-hexane, and title compound 0.55 g (yield 60.9 %) were obtained.

(0264)

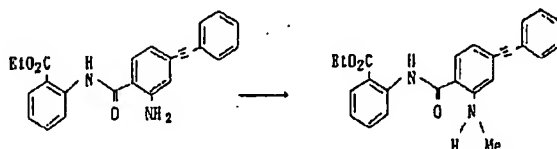
NMR (CDCl₃) delta: 1.43 (3H, t, J = 7 Hz), 4.42 (2H, q, J = 7 Hz), 6.89 (1H, d, J = 1 Hz), 6.92 (1H, dd, J = 8 Hz, 1 Hz), 7.12 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.34-7.38 (3H, m), 7.51-7.56 (2H, m), 7.69 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.70 (1H, d, J = 8 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.89 (1H, s).

(0265)

Reference Example 25

2-(2-methylamino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0266)



(0267)

Potassium carbonate 300 mg (2.24 mmol) and iodo methane 0.2 ml (3.36 mmol) were added to N, N-dimethylformamide (6 ml) solution of 2-(2-amino-4-phenylethynyl benzamide) benzoic acid ethyl ester 0.43 g (1.12 mmol) produced in Reference Example 24, and the mixture was stirred at room temperature for seven hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.24 g (yield 42.0 %) were obtained.

(0268)

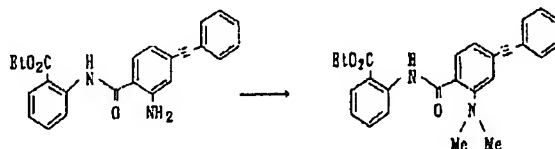
NMR (CDCl₃) delta: 1.43 (3H, t, J = 7 Hz), 2.93 (3H, d, J = 3 Hz), 4.42 (2H, q, J = 7 Hz), 6.84-6.90 (2H, m), 7.08-7.14 (1H, m), 7.34-7.39 (3H, m), 7.54-7.61 (3H, m), 7.72 (1H, d, J = 8 Hz), 7.84-7.94 (1H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.76 (1H, dd, J = 8 Hz, 1 Hz), 11.88 (1H, s).

(0269)

Reference Example 26

2-(2-dimethylamino-4-phenylethynyl benzamide) benzoic acid ethyl ester.

(0270)



(0271)

Potassium carbonate 300 mg (2.24 mmol) and iodo methane 0.2 ml (3.36 mmol) were added to N, N-dimethylformamide (6 ml) solution of 2-(2-amino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester 0.43 g (1.12 mmol) produced in Reference Example 24, and the mixture was stirred at room temperature for 17 hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography with the residue, and title compound 0.29 g (yield 63.0 %) were obtained.

(0272)

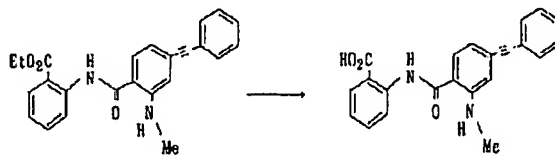
NMR (CDCl₃) delta: 1.39 (3H, t, J = 7 Hz), 2.84 (6H, s), 4.35 (2H, q, J = 7 Hz), 7.11 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.24-7.27 (1H, m), 7.30 (1H, d, J = 1 Hz), 7.34-7.40 (3H, m), 7.53-7.60 (3H, m), 7.94 (1H, d, J = 8 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.91-8.94 (1H, m), 12.59 (1H, s).

(0273)

Example 37

2-(2-methylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0274)



(0275)

1M-sodium hydroxide solution 15 ml were added to ethanol (10 ml) solution of 2-(2-methylamino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester 0.06 g (0.16 mmol) produced in Reference Example 25 and were heated under reflux for four hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 0.05 g (yield 94.0 %) were obtained.

(0276)

NMR (CDCl₃) delta: 2.94 (3H, s), 6.86 (1H, dd, J = 8 Hz, 1 Hz), 6.88 (1H, d, J = 1 Hz), 7.15 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.34-7.40 (3H, m), 7.54-7.59 (2H, m), 7.62-7.67 (1H, m), 7.66 (1H, d, J = 8 Hz), 8.16 (1H, dd, J = 8 Hz, 1 Hz), 8.80 (1H, dd, J = 8 Hz, 1 Hz), 11.66 (1H, s).

IR (ν, cm⁻¹, KBr): 3416, 1690, 1646, 1608, 1584, 1536, 1230, 752.

EI-MS (m/z, %): 370 (m +, 4), 352 (1), 278 (1), 256 (1), 234 (5).

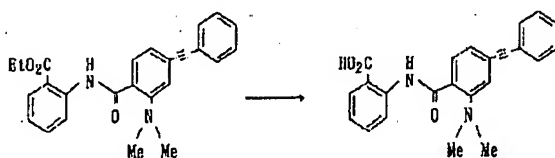
mp: 219-220 degrees.

(0277)

Example 38

2-(2-dimethylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0278)



(0279)

1M-sodium hydroxide solution 10 ml were added to ethanol (10 ml) solution of 2-(2-dimethylamino-4-phenyl-ethynyl benzamide) benzoic acid ethyl ester 0.29 g (0.71 mmol) produced in Reference Example 26 and were heated under reflux for two hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from chloroform-hexane, and title compound 0.19 g (yield 69.4 %) were obtained.

(0280)

NMR (CDCl₃) delta: 2.94 (6H, s), 7.13-7.19 (1H, m), 7.28 (1H, dd, J = 8 Hz, 1 Hz), 7.32 (1H, d, J = 1 Hz), 7.35-7.40 (3H, m), 7.54-7.60 (2H, m), 7.65 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.96 (1H, d, J = 8 Hz), 8.12 (1H, dd, J = 8 Hz, 1 Hz), 8.97 (1H, d, J = 8 Hz), 12.4-12.6 (1H, m).

IR (ν, cm⁻¹, KBr): 1696, 1652, 1586, 1522, 1196, 764, 752.

·EI-MS (m/z, %): 384 (m +, 19), 366 (3), 248 (100), 247 (90), 191 (13), 176(11).

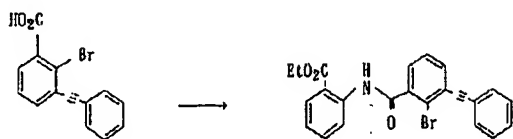
mp: 186-187 degrees.

(0281)

Reference Example 27

2-(2-bromo-3-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0282)



(0283)

Thionyl chloride 1.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene solution (10 ml) of 2-bromo-3-phenyl-ethynyl benzoic acid 1.53 g and were heated under reflux for 45 minutes, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of 5 ml of ethyl acetate and 15 ml of water containing potassium carbonate 1.4 g (10.16 mmol) and 2-ethyl aminobenzoic acid 0.75 ml (5.08 mmol) and it was stirred at room temperature for 17 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 1.80 g (yield 78.9 %) were obtained.

(0284)

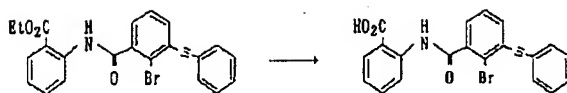
NMR (CDCl₃) delta: 1.39 (3H, t, J = 7 Hz), 4.35 (2H, J = 7 Hz), 7.14-7.20 (1H, m), 7.35-7.43 (4H, m), 7.50 (1H, dd, J = 8 Hz, 1 Hz), 7.57-7.67 (4H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.90 (1H, d, J = 8 Hz), 11.48 (1H, s).

(0285)

Reference Example 28

2-(2-bromo-3-phenyl-ethynyl benzamide) benzoic acid.

(0286)



(0287)

1M-sodium hydroxide solution 20 ml were added to ethanol (20 ml) solution of 2-(2-bromo-3-phenyl-ethynyl benzamide) benzoic acid ethyl ester 1.79 g (3.99 mmol) produced in Reference Example 27, and it was heated with stirring for two hours, and next ethanol was eliminated by distillation under reduced pressure. Concentrated hydrochloric acid was dropwise-added under ice cooling to the residue, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 1.52 g (yield 90.5 %) were obtained.

(0288)

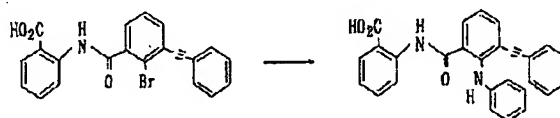
NMR (DMSO-d₆) delta: 7.23-7.29 (1H, m), 7.44-7.52 (3H, m), 7.56-7.72 (5H, m), 7.81 (1H, dd, J = 8 Hz, 1 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.57 (1H, d, J = 8 Hz).

(0289)

Example 39

2-(2-phenylamino-3-phenyl-ethynyl benzamide) benzoic acid.

(0290)



(0291)

Potassium carbonate 0.11 g (0.80 mmol) and 5 wt.% activated copper was added to aniline (2 ml) solution of 2-(2-bromo-3-phenyl-ethynyl benzamide) benzoic acid 0.30 g (0.71 mmol) produced in Reference Example 28, and it was heated with stirring at 180 degrees for two hours and next was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate,

and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethyl acetate-hexane, and title compound 0.17 g (yield 56.3 %) were obtained.

(0292)

NMR (CDCl₃) delta: 6.82 (1H, s), 6.93-6.98 (1H, m), 7.03-7.10 (3H, m), 7.14-7.28 (8H, m), 7.38 (1H, dd, J = 7.1 Hz), 7.43-7.48 (1H, m), 7.79 (1H, dd, J = 8 Hz, 1 Hz), 7.97 (1H, dd, J = 8 Hz, 1 Hz), 8.26 (1H, d, J = 8 Hz), 10.82 (1H

IR (ν, cm⁻¹, KBr): 688, 1636, 1604, 1524, 1240, 762, 740, 698.

EI-MS (m/z, %): 32 (m +, 67), 414 (5), 296 (100), 267 (29).

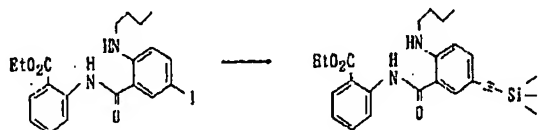
mp: 57-258 degrees.

(0293)

Reference Example 29

2-(2-butylamino-5-trimethylsilyl ethynyl benzamide) benzoic acid ethyl ester.

(0294)



(0295)

Trimethylsilylacetylene 2.3 ml (16.59 mmol), dichlorobis triphenylphosphine palladium 90 mg (0.13 mmol) and copper iodide 50 mg (0.26 mmol) were added to diethylamine (80 ml) solution of 2-(2-butylamino 5-iodobenzamide) benzoic acid ethyl ester 6.45 g (13.82 mmol) and were stirred at room temperature for one hour 30 minutes, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 4.5 g (yield 74.6 %) were obtained.

(0296)

NMR (CDCl₃) delta: 0.25 (9H, s), 0.96 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.42-1.50 (2H, m), 1.62-1.71 (2H, m), 3.14-3.22 (2H, m), 4.42 (2H, q, J = 7 Hz), 6.63 (1H, d, J = 9 Hz), 7.11 (1H, ddd, J

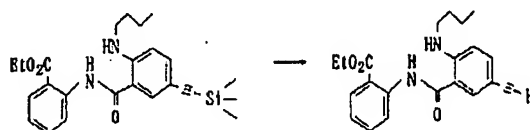
= 8 Hz, 7 Hz, 1 Hz), 7.42 (1H, dd, J = 9 Hz, 2 Hz), 7.57 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.86 (1H, d, J = 2 Hz), 7.95-8.01 (1H, m), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.65 (1H, dd, J = 8 Hz, 1 Hz), 11.69 (1H, s).

(0297)

Reference Example 30

2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester.

(0298)



(0299)

1M-tetrabutyl ammonium fluoride tetrahydrofuran solution 11 ml (11.0 mmol) were added to tetrahydrofuran (60 ml) solution of 2-(2-butylamino-5-trimethylsilylethynyl benzamide) benzoic acid ethyl ester 4.36 g (9.99 mmol) produced in Reference Example 29, and it was stirred under ice cooling for one hour. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 3.06 g (yield 84.0 %) were obtained.

(0300)

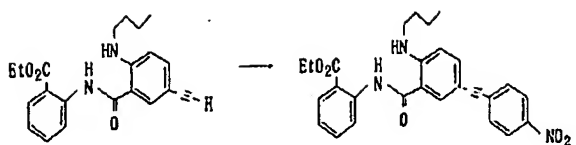
NMR (CDCl₃) delta: 0.96 (3H, t, J = 7 Hz), 1.40-1.52 (5H, m), 1.64-1.72 (2H, m), 2.99 (1H, s), 3.16-3.23 (1H, m), 4.43 (2H, q, J = 7 Hz), 6.65 (1H, d, J = 9 Hz), 7.11 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.44 (1H, dd, J = 9 Hz, 2 Hz), 7.57 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.88 (1H, d, J = 2 Hz), 7.98-8.06 (1H, m), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.68 (1H, dd, J = 8 Hz, 1 Hz), 11.77 (1H, s).

(0301)

Reference Example 31

2-(2-butylamino-5-(4-nitrophenyl) ethynyl benzamide) benzoic acid ethyl ester.

(0302)



(0303)

4-iodo nitrobenzene 270 ml (1.09 mmol), dichlorobis triphenylphosphine palladium 14 mg (0.01 mmol) and copper iodide 8 mg (0.02 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 300 mg (0.82 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for one hour, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 383 mg (yield 95.8 %) were obtained.

(0304)

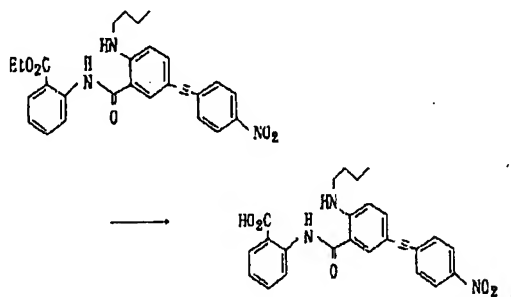
NMR (CDCl₃) delta: 0.98 (3H, t, J = 7 Hz), 1.40-1.55 (5H, m), 1.63-1.74 (2H, m), 3.17-3.26 (2H, m), 4.43 (2H, q, J = 7 Hz), 6.71 (1H, d, J = 9 Hz), 7.11-7.16 (1H, m), 7.51 (1H, dd, J = 9 Hz, 2 Hz), 7.57-7.65 (3H, m), 7.95 (1H, d, J = 2 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.20 (2H, d, J = 9 Hz), 8.68 (1H, d, J = 8 Hz), 11.82 (1H, s).

(0305)

Example 40

2-(2-butylamino-5-(4-nitrophenyl) ethynyl benzamide) benzoic acid.

(0306)



(0307)

1M-sodium hydroxide solution 2 ml were added to dioxane (10 ml) solution of 2-(2-butylamino-5-(4-nitrophenyl) ethynyl benzamide) benzoic acid ethyl ester 250 mg (0.51 mmol) produced in Reference Example 31, and the mixture was stirred at room temperature for 18 hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 210 mg (yield 86.4 %) were obtained.

(0308)

NMR (CDCl₃) delta: 0.99 (3H, t, J = 7 Hz), 1.44-1.54 (2H, m), 1.67-1.76 (2H, m), 3.24 (2H, t, J = 7 Hz), 6.72 (1H, d, J = 9 Hz), 6.99-7.05 (1H, m), 7.50 (1H, dd, J = 9 Hz, 2 Hz), 7.58 (2H, d, J = 9 Hz, 2 Hz), 7.63 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.92 (1H, d, J = 2 Hz), 8.04 (1H, dd, J = 8 Hz, 1 Hz), 8.09 (2H, d, J = 9 Hz), 8.18-8.30 (1H, m), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.63 (1H, s).

IR (ν, cm⁻¹, KBr): 3452, 2964, 2196, 1658, 1588, 1520, 1340, 1258, 1218, 856, 748.

El-MS (m/z, %): 457 (m⁺, 14), 439 (89), 410 (25), 396 (66), 368 (18), 350 (13), 321 (100).

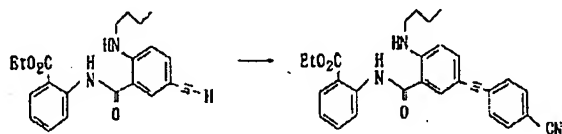
mp: 179-180 degrees.

(0309)

Reference Example 32

2-(2-butylamino-5-(4-cyanophenyl) ethynyl benzamide) benzoic acid ethyl ester.

(0310)



(0311)

4-iodo benzonitrile 250 mg (1.09 mmol), dichlorobis triphenylphosphine palladium 14 mg (0.01 mmol) and copper iodide 8 mg (0.02 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 300 mg (0.82 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for two hours, and next

diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 210 mg (yield 54.7 %) were obtained.

(0312)

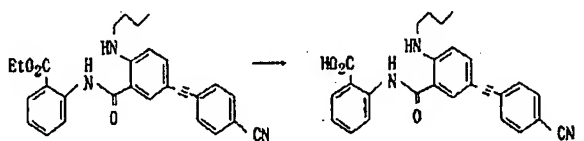
NMR (CDCl₃) delta: 0.97 (3H, t, J = 7 Hz), 1.40-1.52 (5H, m), 1.64-1.74 (2H, m), 3.22 (2H, dt, J = 7 Hz, 5 Hz), 4.43 (2H, q, J = 7 Hz), 6.70 (1H, d, J = 9 Hz), 7.11-7.16 (1H, m), 7.45-7.52 (1H, m), 7.55-7.64 (5H, m), 7.93 (1H, d, J = 2 Hz), 8.08-8.16 (2H, m), 8.68 (1H, dd, J = 8 Hz, 1 Hz), 11.80 (1H, s).

(0313)

Example 41

2-(2-butylamino-5-(4-cyanophenyl) ethynyl benzamide) benzoic acid.

(0314)



(0315)

1M-sodium hydroxide solution 5 ml were added to dioxane (10 ml) solution of 2-(2-butylamino-5-(4-cyanophenyl) ethynyl benzamide) benzoic acid ethyl ester 210 mg (0.45 mmol) produced in Reference Example 32, and the mixture was stirred at room temperature for 24 hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 120 mg (yield 61.0 %) were obtained.

(0316)

NMR (CDCl₃) delta: 0.99 (3H, t, J = 7 Hz), 1.41-1.54 (2H, m), 1.67-1.75 (2H, m), 3.23 (2H, t, J = 7 Hz), 6.71 (1H, d, J = 9 Hz), 7.03-7.09 (1H, m), 7.49 (1H, dd, J = 9 Hz, 2 Hz), 7.52-7.56 (4H, m),

7.65 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.91 (1H, d, J = 2 Hz), 8.05 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.67 (1H, s).

IR (ν , cm⁻¹, KBr): 2964, 2248, 2204, 1654, 1598, 1530, 1298, 1218, 834, 756.

EI-MS (m/z, %): 437 (m +, 1), 419 (100), 390 (24), 376 (85), 348 (24).

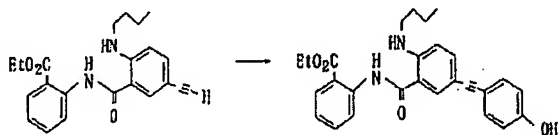
mp: 197-198 degrees.

(0317)

Reference Example 33

2-(2-butylamino-5-(4-hydroxyphenyl) ethynyl benzamide) benzoic acid ethyl ester.

(0318)



(0319)

4-t-butyl dimethylsilyloxy iodo benzene 410 ml (1.23 mmol), dichlorobis triphenylphosphine palladium 14 mg (0.01 mmol) and copper iodide 8 mg (0.02 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 300 mg (0.82 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for 19 hours, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and thereafter, tetrahydrofuran (10 ml) was added, and 1M-tetrabutyl ammonium fluoride tetrahydrofuran solution 1.3 ml (1.3 mmol) were added, and it was stirred with ice cooling for one hour. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 184 mg (yield 49.0 %) were obtained.

(0320)

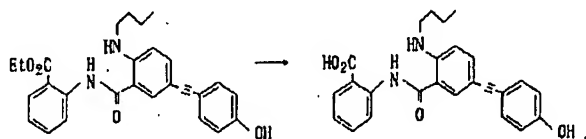
NMR (CDCl₃) delta: 0.97 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.44-1.54 (2H, m), 1.62-1.72 (2H, m), 3.17-3.26 (2H, m), 4.43 (2H, q, J = 7 Hz), 4.90 (1H, s), 6.68 (1H, d, J = 9 Hz), 6.80 (2H, d, J = 9 Hz), 7.09-7.14 (1H, m), 7.41 (2H, d, J = 9 Hz), 7.47 (1H, dd, J = 9 Hz, 2 Hz), 7.55-7.61 (1H, m), 7.88 (1H, d, J = 2 Hz), 7.94-8.00 (1H, m), 8.09 (1H, dd, 8 Hz, 1 Hz), 8.67 (1H, d, J = 8 Hz), 11.74 (1H, s).

(0321)

Example 42

2-(2-butylamino-5-(4-hydroxyphenyl) ethynyl benzamide) benzoic acid.

(0322)



(0323)

1M-sodium hydroxide solution 10 ml were added to dioxane (20 ml) solution of 2-(2-butylamino-5-(4-hydroxyphenyl) ethynyl benzamide) benzoic acid ethyl ester 180 mg (0.39 mmol) produced in Reference Example 33, and the mixture was stirred at room temperature for four hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 116 mg (yield 56.7 %) were obtained.

(0324)

NMR (DMSO-d₆) delta: 0.94 (3H, t, J = 7 Hz), 1.36-1.46 (2H, m), 1.56-1.64 (2H, m), 3.18-3.24 (2H, m), 6.76-6.84 (3H, m), 7.18-7.24 (1H, m), 7.32 (2H, d, J = 9 Hz), 7.48 (1H, dd, J = 9 Hz, 2 Hz), 7.61-7.67 (1H, m), 7.84 (1H, d, J = 2 Hz), 8.00-8.07 (2H, m), 8.53 (1H, dd, J = 8 Hz, 1 Hz), 11.96 (1H, s)

IR (ν, cm⁻¹, KBr): 3336, 2964, 1648, 1606, 1526, 1256, 1210, 836, 762.

El-MS (m/z, %): 428 (m +, 4), 410 (100), 381 (6), 367 (17), 321 (20).

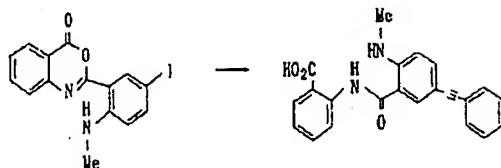
mp: 197-198 degrees.

(0325)

Example 43

2-(2-methylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0326)



(0327)

Ethynylbenzene 0.2 ml (1.72 mmol), dichlorobis triphenylphosphine palladium 10 mg (0.01 mmol) and copper iodide 6 mg (0.02 mmol) were added to triethylamine (10 ml) and tetrahydrofuran (15 ml) solution of 2-(2-methylamino-5-iodophenyl)-4-oxo-4H-3,1-benzoxazine 500 mg (1.32 mmol), and under a nitrogen atmosphere, it was stirred at room temperature for four hours, and next triethylamine was eliminated by distillation under reduced pressure. Saturated aqueous sodium bicarbonate solution was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in 20 ml dioxane, and 1M-sodium hydroxide solution 10 ml were added, and the mixture was stirred at room temperature for 18 hours, and next dioxane was eliminated by distillation under reduced pressure. 2M-hydrochloric acid was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 340 mg (yield 69.7 %) were obtained.

(0328)

NMR (DMSO-d₆) delta: 2.28 (3H, d, J = 5 Hz), 6.79 (1H, d, J = 9 Hz), 7.18-7.24 (1H, m), 7.38-7.46 (3H, m), 7.48-7.53 (2H, m), 7.56 (1H, dd, J = 9 Hz, 2 Hz), 7.65 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.88 (1H, d, J = 2 Hz), 7.90-7.96 (1H, m), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.54 (1H, dd, J = 8 Hz, 1 Hz), 11.93 (1H, s).

IR (ν, cm⁻¹, KBr): 3404, 2208, 1664, 1528, 1214, 756.

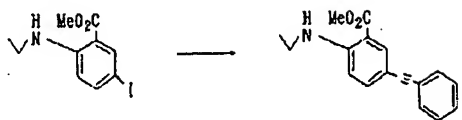
EI-MS (m/z, %): 370 (m +, 100), 352 (48), 323 (7), 233 (62) mp. 205-206 degrees.

(0329)

Reference Example 34

2-ethylamino-5-phenyl-ethynyl methyl benzoate ester.

(0330)



(0331)

Ethynylbenzene 1.0 ml (9.43 mmol), dichlorobis triphenylphosphine palladium 55 mg (0.08 mmol) and copper iodide 30 mg (0.16 mmol) were added to diethylamine (25 ml) solution of 2-ethylamino-5-iodobenzoic acid methyl 2.24 g (7.86 mmol), and the mixture was stirred at room temperature for 24 hours, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution; and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 1.26 g (yield 57.4 %) were obtained.

(0332)

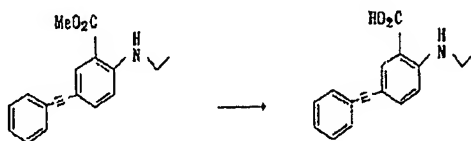
NMR (CDCl₃) delta: 1.33 (3H, t, J = 7 Hz), 3.26 (2H, ddd, J = 14 Hz, 7 Hz, 5 Hz), 6.65 (1H, d, J = 9 Hz), 7.28-7.35 (3H, m), 7.46-7.52 (3H, m), 7.80-7.86 (1H, m), 8.11 (1H, d, J = 2 Hz).

(0333)

Reference Example 35

2-ethylamino-5-phenyl-ethynyl benzoic acid.

(0334)



(0335)

1M-sodium hydroxide solution 10 ml were added to ethanol (20 ml) solution of 2-ethylamino-5-phenyl-ethynyl methyl benzoate 1.26 g (4.51 mmol) produced in Reference Example 34 and were heated under reflux for three hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. 2M-hydrochloric acid solution was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 0.96 g (yield 80.2 %) were obtained.

(0336)

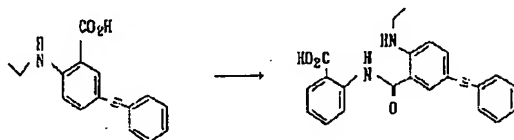
NMR (DMSO-d₆) delta: 1.22 (3H, t, J = 7 Hz), 3.25 (2H, q, J = 7 Hz), 6.77 (1H, d, J = 9 Hz), 7.36-7.43 (3H, m), 7.48-7.55 (3H, m), 7.94 (1H, d, J = 2 Hz).

(0337)

Example 44

2-(2-ethylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0338)



(0339)

Thionyl chloride 0.13 ml (1.81 mmol) were added under a nitrogen atmosphere to anhydrous benzene solution (15 ml) of 2-ethylamino-5-phenyl-ethynyl benzoic acid 400 mg (1.51 mmol) produced in Reference Example 35 and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. To anhydrous toluene (20 ml) solution of the residue, 2-aminobenzoic acid 0.25 g (1.51 mmol) and potassium carbonate 0.21 g (1.81 mmol) were added and under a nitrogen atmosphere, were heated under reflux for seven hours and thereafter, were cooled to room temperature. Water was added to the reaction solution, and thereafter, the organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by

distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 0.25 g (yield 60.4 %) were obtained.

(0340)

NMR (DMSO-d₆) delta: 1.23 (3H, t, J = 7 Hz), 3.20-3.26 (2H, m), 6.83 (1H, d, J = 9 Hz), 7.18-7.24 (1H, m), 7.37-7.46 (3H, m), 7.48-7.56 (3H, m), 7.62-7.68 (1H, m), 7.89 (1H, d, J = 2 Hz), 7.93-8.00 (1H, m), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.52 (1H, dd, J = 8 Hz, 1 Hz), 11.95 (1H, s) IR (ν, cm⁻¹, KBr): 3328, 2972, 2212, 1654, 1534, 1252, 1222, 756.

El-MS (m/z, %): 384 (m +, 100), 366 (92), 337 (22), 323 (27), 247 (44), 232 (25).

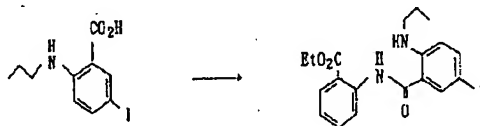
mp: 202-204 degrees.

(0341)

Reference Example 36

2-(2-propylamino-5-iodo benzamide) benzoic acid ethyl ester.

(0342)



(0343)

Thionyl chloride 0.34 ml (4.72 mmol) were added under a nitrogen atmosphere to anhydrous benzene solution (20 ml) of 2-propylamino-5-iodobenzoic acid 1.2 g (3.93 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. To anhydrous toluene (30 ml) solution of the residue, 2-ethyl aminobenzoic acid 0.7 ml (4.72 mmol) and potassium carbonate 0.65 g (4.72 mmol) were added and under a nitrogen atmosphere, it was heated under reflux for seven hours and thereafter, was cooled to room temperature. Water was added to the reaction solution, and thereafter, the organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 1.0 g (yield 56.3 %) were obtained.

(0344)

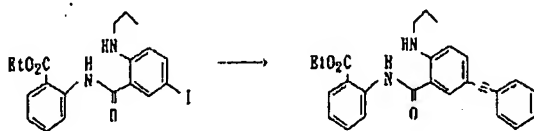
NMR (CDCl₃) delta: 1.02 (3H, t, J = 7 Hz), 1.45 (3H, t, J = 7 Hz), 1.70 (2H, hex, J = 7 Hz), 3.12 (2H, dt, J = 7.5 Hz), 4.44 (2H, q, J = 7 Hz), 6.50 (1H, d, J = 9 Hz), 7.11 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.52-7.60 (2H, m), 7.75-7.84 (1H, m), 7.96 (1H, d, J = 2 Hz), 8.09 (1H, dd, J = 8 Hz, 1 Hz), 8.67 (1H, dd, J = 8 Hz, 1 Hz), 11.74 (1H, s).

(0345)

Reference Example 37

2-(2-propylamino-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0346)



(0347)

Ethynylbenzene 0.16 ml (1.78 mmol), dichlorobis triphenylphosphine palladium 10 mg (0.01 mmol) and copper iodide 6 mg (0.02 mmol) were added to diethylamine (10 ml) solution of 2-(2-propylamino-5-iodo benzamide) benzoic acid ethyl ester 500 mg (1.10 mmol) produced in Reference Example 36, and the mixture was stirred at room temperature for 20 hours, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 0.38 g (yield 81.8 %) were obtained.

(0348)

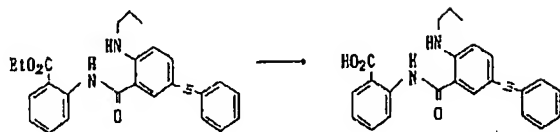
NMR (CDCl₃) delta: 1.04 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.72 (2H, Hex, J = 7 Hz), 3.18 (2H, dt, J = 7.5 Hz), 4.43 (2H, q, J = 7 Hz), 6.69 (1H, d, J = 9 Hz), 7.12 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.28-7.36 (3H, m), 7.47-7.53 (3H, m), 7.58 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.92 (1H, d, J = 2 Hz), 8.00-8.06 (1H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.68 (1H, dd, J = 8 Hz, 1 Hz), 11.77 (1H, s).

(0349)

Example 45

2-(2-propylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0350)



(0351)

1M-sodium hydroxide solution 10 ml were added to dioxane (20 ml) solution of 2-(2-propylamino-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 380 mg (0.89 mmol) produced in Reference Example 37, and the mixture was heated under reflux for four hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 250 mg (yield 70.5 %) were obtained.

(0352)

NMR (DMSO-d₆) delta: 0.98 (3H, t, J = 7 Hz), 1.63 (2H, hex, J = 7 Hz), 3.14-3.24 (2H, m), 6.83 (1H, d, J = 9 Hz), 7.18-7.25 (1H, m), 7.38-7.45 (3H, m), 7.48-7.56 (3H, m), 7.60-7.68 (1H, m), 7.90 (1H, d, J = 2 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.07-8.12 (1H, m), 8.52 (1H, d, J = 8 Hz), 11.95 (1H, s).

IR (v, cm⁻¹, KBr): 3324, 2212, 1658, 1532, 1254, 1220, 756.

EI-MS (m/z, %): 398 (m +, 100), 380 (35), 351 (27), 323 (7), 232 (58).

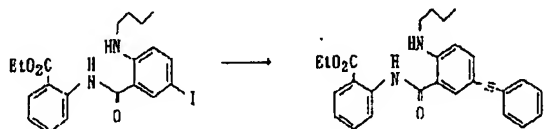
mp: 193-194 degrees.

(0353)

Reference Example 38

2-(2-butylamino-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0354)



(0355)

Ethynylbenzene 0.16 ml (1.78 mmol), dichlorobis triphenylphosphine palladium 10 mg (0.01 mmol) and copper iodide 6 mg (0.02 mmol) were added to diethylamine (10 ml) solution of ethyl 2-(2-butylamino-5-iodobenzamide) benzoic acid ethyl ester 500 mg (1.07 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for 19 hours, and next diethylamine was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 0.38 g (yield 80.6 %) were obtained.

(0356)

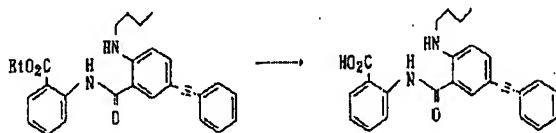
NMR (CDCl₃) delta: 0.97 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.43-1.52 (2H, m), 1.64-1.74 (2H, m), 3.18-3.26 (2H, m), 4.42 (2H, q, J = 7 Hz), 6.69 (1H, d, J = 9 Hz), 7.09-7.14 (1H, m), 7.26-7.36 (3H, m), 7.47-7.54 (3H, m), 7.54-7.62 (1H, m), 7.91 (1H, d, J = 2 Hz), 7.97-8.04 (1H, m), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.68 (1H, dd, J = 8 Hz, 1 Hz), 11.76 (1H, s).

(0357)

Example 46

2-(2-butylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0358)



(0359)

1M-sodium hydroxide solution 10 ml were added to dioxane (20 ml) solution of 2-(2-butylamino-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 380 mg (0.86 mmol) produced in Reference Example 38, and the mixture was heated under reflux for 6 hours. 2M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was

eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 294 mg (yield 82.7 %) were obtained.

(0360)

NMR (CDCl₃) delta: 0.98 (3H, t, J = 7 Hz), 1.48 (2H, hex, J = 7 Hz), 1.6-1.74 (2H, m), 3.22 (2H, t, J = 7 Hz), 6.71 (1H, d, J = 9 Hz), 6.93-6.98 (1H, m), 7.23-7.30 (2H, m), 7.48-7.54 (3H, m), 7.60 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.91 (1H, d, J = 2 Hz), 8.00 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz), 11.68 (1H, s).

IR (ν, cm⁻¹, KBr): 3368, 3320, 2964, 2216, 1652, 1528, 1252, 1218, 756.

EI-MS (m/z, %): 412 (m +, 100), 394 (26), 351 (22), 323 (7), 232 (71).

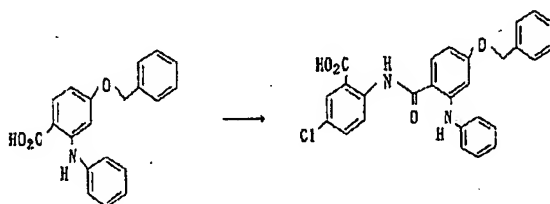
mp: 188-189 degrees.

(0361)

Example 47

5-chloro-2-(4-benzyloxy-2-phenylamino benzamide) benzoic acid.

(0362)



(0363)

To methylene chloride (10 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 0.50 g (1.56 mmol), thionyl chloride 0.28 g (2.35 mmol) was added under a nitrogen atmosphere, and it was stirred under ice cooling for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (10 ml) solution of the residue was dropwise-added to 2-amino-5-chlorobenzoic acid 0.40 g (2.35 mmol) and methylene chloride (15 ml) solution of triethylamine 0.65 ml (2.35 mmol) and was stirred at room temperature for 17 hours. Water was added to the reaction solution, and extraction was carried out with methylene chloride. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from silica gel chromatography and acetonitrile, and title compound 390 mg (yield 53.0 %) were obtained.

(0364)

NMR (DMSO-d₆) delta: 5.14 (2H, s), 6.62 (1H, dd, J = 9 Hz, 2 Hz), 6.80 (1H, d, J = 2 Hz), 7.02 (1H, t, J = 7 Hz), 7.12 (2H, d, J = 7 Hz), 7.25-7.41 (7H, m), 7.69 (1H, dd, J = 9 Hz, 2 Hz), 7.74 (1H, d, J = 9 Hz), 7.96 (1H, d, J = 2 Hz), 8.59 (1H, d, J = 9 Hz), 9.70 (1H, s), 11.87 (1H, s).

IR (ν, cm⁻¹, KBr): 1652, 1582, 1434, 1256, 752.

EI-MS (m/z, %): 472 (m +, 6), 386 (15), 329 (13), 301 (7), 251 (10), 119 (10), 91 (100).

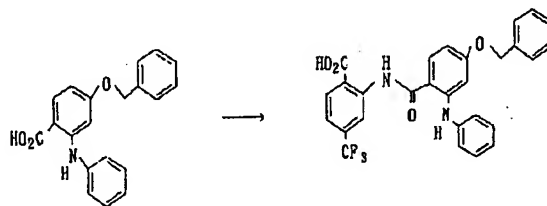
mp: 229-230 degrees.

(0365)

Example 48

2-(4-benzyloxy-2-phenylamino benzamide)-4-trifluoromethyl benzoic acid.

(0366)



(0367)

To methylene chloride (15 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 500 mg (1.56 mmol), thionyl chloride 186 mg (1.56 mmol) was added, and it was stirred under ice cooling for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (10 ml) solution of the residue was dropwise-added to methylene chloride (15 ml) suspending solution of 2-amino-4-trifluoromethyl benzoic acid 480 mg (2.35 mmol) and potassium carbonate 539 mg (3.9 mmol), and it was stirred for one hour, and thereafter, triethylamine 1 ml (2.35 mmol) was added, and it was stirred at room temperature furthermore for 15 hours. 1M-hydrochloric acid was added to the reaction solution, and the organic layer was extracted with methylene chloride. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from silica gel chromatography and acetonitrile, and title compound 370 mg (yield 46.5 %) were obtained.

(0368)

NMR (DMSO-d₆) delta: 5.13 (2H, s), 6.64 (1H, dd, J = 9 Hz, 2 Hz), 6.79 (1H, d, J = 2 Hz), 7.03 (1H, t, J = 7 Hz), 7.14 (2H, dd, J = 8 Hz, 1 Hz), 7.27-7.44 (7H, m), 7.53 (1H, dd, J = 8 Hz, 1 Hz), 7.76 (1H, d, J = 9 Hz), 8.21 (1H, d, J = 8 Hz), 8.95 (1H, d, J = 1 Hz), 9.60 (1H, s), 12.00 (1H, s).

IR (ν, cm⁻¹, KBr): 1645, 1597, 1573, 1521, 1233, 749.

EI-MS (m/z, %): 506 (m +, 53), 488 (9), 446 (4), 329 (5), 302 (17), 301 (39), 300 (16), 272 (9), 211 (7), 91 (100).

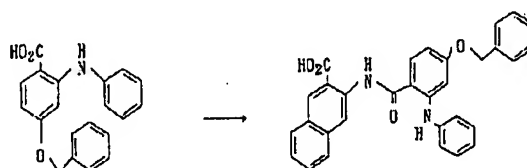
mp: 207-208 degrees.

(0369)

Example 49

3-(4-benzyloxy-2-phenylamino benzamide)-2-naphthalenecarboxylic acid.

(0370)



(0371)

To methylene chloride (10 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 500 mg (1.56 mmol), thionyl chloride 186 mg (1.56 mmol) were added under ice cooling and were stirred for two hours. This solution was dropwise-added to 3-amino-2 naphthalenecarboxylic acid 438 mg (2.34 mmol) and methylene chloride (15 ml) solution of triethylamine 1.09 ml (7.83 mmol) and was stirred at room temperature for three days. The reaction solution was acidified with 1M-hydrochloric acid, and extraction was carried out with acetic acid ethyl ester. It was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from ethanol, and title compound 438 mg (yield 57.0 %) were obtained.

(0372)

NMR (DMSO-d₆) delta: 5.15 (2H, s), 6.64 (1H, dd, J = 9 Hz, 2 Hz), 6.83 (1H, d, J = 2 Hz), 7.03 (1H, t, J = 7 Hz), 7.15 (2H, d, J = 8 Hz), 7.29-7.42 (7H, m), 7.50 (1H, t, J = 7 Hz), 7.63 (1H, t, J = 8 Hz), 7.81 (1H, d, J = 9 Hz), 7.94 (1H, d, J = 8 Hz), 8.05 (1H, d, J = 8 Hz), 8.74 (1H, s), 9.04 (1H, s), 9.87 (1H, s), 12.06 (1H, s).

IR (ν, cm⁻¹, KBr): 3352, 1694, 1642, 1546, 1254, 740.

EI-MS (m/z, %): 488 (m +,5), 446 (9), 386 (6), 330 (5), 329 (10), 328 (5), 251(11), 129 (9), 121 (9), 119 (10), 97 (8), 91 (72).

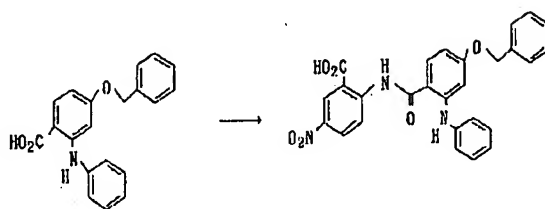
mp: 268 degrees.

(0373)

Example 50

2-(4-benzyloxy-2-phenylamino benzamide)-5-nitrobenzoic acid.

(0374)



(0375)

To methylene chloride (10 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 580 mg (1.82 mmol), thionyl chloride 324 mg (2.72 mmol) was added under ice cooling, and it was stirred with ice cooling for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (10 ml) solution of the residue was dropwise-added to 2-amino-5-nitrobenzoic acid 365 mg (2.00 mmol) and methylene chloride (10 ml) solution of triethylamine 0.76 ml (5.46 mmol) and was stirred at room temperature for 20 hours. Water was added to the reaction solution and was extracted with methylene chloride. It was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from silica gel chromatography and acetonitrile, and title compound 440 mg (yield 50.0 %) were obtained.

(0376)

NMR (DMSO-d₆) delta: 5.04 (2H, s), 6.51 (1H, dd, J = 9 Hz, 2 Hz), 6.82 (1H, d, J = 2 Hz), 7.10 (1H, dd, J = 7 Hz, 7 Hz), 7.17 (2H, dd, J = 8 Hz, 1 Hz), 7.30-7.41 (7H, m), 8.45 (1H, dd, J = 9 Hz, 2 Hz), 7.72 (1H, d, J = 9 Hz), 9.00-9.10 (2H, s), 9.91 (1H, s), 11.99 (1H, s).

IR (ν, cm⁻¹, KBr): 1694, 1658, 1550, 1228, 756, 744.

FAB-MS (m/z, %): 484 (M-H, 3), 302 (100).

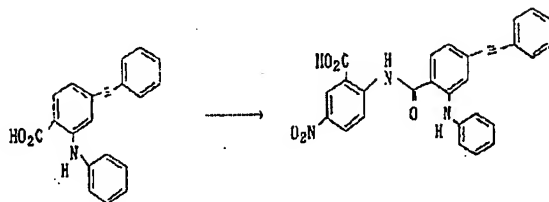
mp: 202-203 degrees.

(0377)

Example 51

5-nitro-2-(2-phenylamino 4-phenyl-ethynyl benzamide) benzoic acid.

(0378)



(0379)

To methylene chloride (10 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 200 mg (0.64 mmol), thionyl chloride 114 mg (0.96 mmol) was added under ice cooling, and it was stirred with ice cooling for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (10 ml) solution of the residue was dropwise-added to 2-amino-5-nitrobenzoic acid 174 mg (0.96 mmol) and methylene chloride (10 ml) solution of triethylamine 0.26 ml (1.91 mmol) and was stirred at room temperature for 20 hours. Water was added to the reaction solution and was extracted with methylene chloride. It was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from silica gel chromatography and acetonitrile, and title compound 92 mg (yield 30.0 %) were obtained.

(0380)

NMR (DMSO-d₆) delta: .07 (1H, t, J = 7 Hz), 7.13 (1H, dd, J = 8 Hz, 1 Hz), 7.23 (2H, d, J = 7 Hz), 7.34-7.59 (8H, m), 7.83 (1H, d, J = 8 Hz), 8.49 (1H, dd, J = 9 Hz, 3 Hz), 8.76 (1H, d, J = 3 Hz), 8.84 (1H, d, J = 9 Hz), 9.27 (1H, s), 12.48 (1H, s).

IR (ν, cm⁻¹, KBr): 2212, 1704, 1636, 1596, 1514, 1220, 762.

FAB-MS (m/z, %): 476 (M-H, 100).

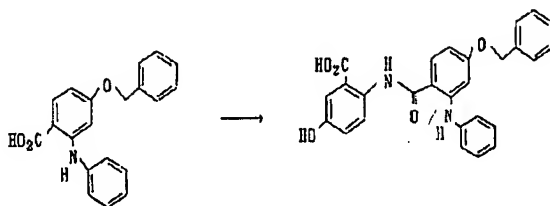
mp: 248-250 degrees.

(0381)

Example 52

2-(4-benzyloxy-2-phenylamino benzamide)-5-hydroxybenzoic acid.

(0382)



(0383)

To methylene chloride (10 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 500 mg (1.56 mmol), it was added thionyl chloride 0.15 ml (2.00 mmol), and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. To toluene (20 ml) solution of the residue, 2-amino-5-hydroxybenzoic acid 240 mg (1.56 mmol) and potassium carbonate 330 mg (2.39 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography and recrystallisation from acetonitrile, and title compound 243 mg (yield 34.0 %) were obtained.

(0384)

NMR (DMSO-d₆) delta: 5.13 (2H, s), 6.59 (1H, dd, J = 9 Hz, 2 Hz), 6.80 (1H, d, J = 2 Hz), 6.98-7.04 (2H, m), 7.11 (2H, d, J = 8 Hz), 7.25-7.43 (8H, m), 7.72 (1H, d, J = 9 Hz), 8.31 (1H, d, J = 9 Hz), 9.61 (1H, s), 9.83 (1H, s), 11.62 (1H, m).

IR (ν, cm⁻¹, KBr): 3364, 1668, 1644, 1614, 1588, 1546, 1524, 1498, 1472, 1288, 1252, 1226, 1192, 762, 740.

FAB-MS (m/z, %): 453 (M-H, 100)

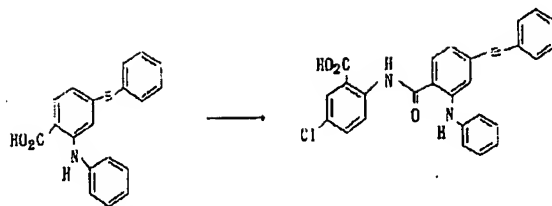
mp. 212-214 degrees.

(0385)

Example 53

5-chloro-2-(2-phenylamino 4-phenyl-ethynyl benzamide) benzoic acid.

(0386)



(0387)

To methylene chloride (15 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 250 mg (0.80 mmol), thionyl chloride 0.07 ml (0.96 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To toluene (20 ml) solution of the residue, 2-amino-5-chlorobenzoic acid 171 mg (1.0 mmol) and potassium carbonate 276 mg (2.0 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and it was obtained title compound 300 mg (yield 80.0 %).

(0388)

NMR (DMSO-d₆) delta: 7.06 (1H, t, J = 7 Hz), 7.11 (1H, dd, J = 8 Hz, 1 Hz), 7.22 (2H, d, J = 7 Hz), 7.33-7.39 (3H, m), 7.41-7.46 (3H, m), 7.54-7.59 (2H, m), 7.71 (1H, dd, J = 9 Hz, 2 Hz), 7.80 (1H, d, J = 8 Hz), 7.97 (1H, d, J = 2 Hz), 8.57 (1H, d, J = 9 Hz), 9.30 (1H, s), 12.00 (1H, s).

IR (ν, cm⁻¹, KBr): 3384, 3208, 1704, 1636, 1608, 1580, 1550, 1518, 1496, 1286, 1222, 1222, 1188, 750, 692.

EI-MS (m/z, %): 466 (m +, 4), 296 (6), 295 (10), 91 (100).

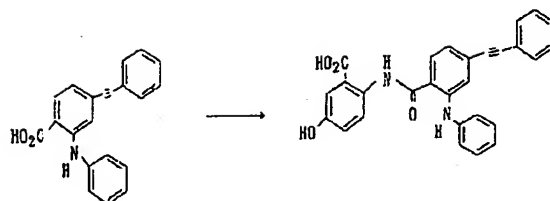
mp: 256-257 degrees.

(0389)

Example 54

5-hydroxy-2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0390)



(0391)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 500 mg (1.60 mmol), thionyl chloride 0.15 ml (2.00 mmol) was added, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. To toluene (50 ml) solution of the residue, 2-amino-5-hydroxybenzoic acid 294 mg (1.92 mmol) and potassium carbonate 266 mg (1.92 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and title compound 500 mg (yield 70.0 %) were obtained.

(0392)

NMR (DMSO-d₆) delta: 7.03-7.13 (3H, m), 7.23 (2H, dd, J = 8 Hz, 1 Hz), 7.34-7.45 (7H, m), 7.54-7.59 (2H, m), 7.79 (1H, d, J = 8 Hz), 8.29 (1H, d, J = 9 Hz), 9.41 (1H, s), 9.68 (1H, s), 11.58 (1H, s), 13.58 (1H, m).

IR (ν, cm⁻¹, KBr): 3344, 3048, 1680, 1648, 1588, 1534, 1498, 1416, 1290, 1254, 1220, 754.

FAB-MS (m/z, %): 447 (M-H, 100).

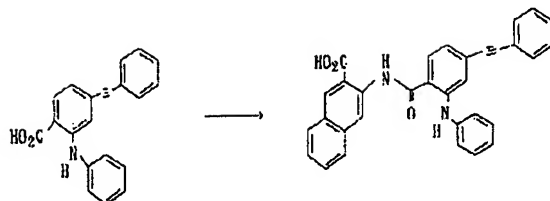
mp: 233-234 degrees.

(0393)

Example 55

3-(2-phenylamino-4-phenyl-ethynyl benzamide)-2-naphthalenecarboxylic acid.

(0394)



(0395)

To methylene chloride (25 ml) solution of 2-phenylamino-4-phenylethynyl benzoic acid 500 mg (1.60 mmol), thionyl chloride 0.4 ml (1.92 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To toluene (50 ml) solution of the residue, 3-amino-2-naphthalenecarboxylic acid 450 mg (1.92 mmol) and potassium carbonate 265 mg (1.92 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography and methanol washing, and title compound 286 mg (yield 37.0 %) were obtained.

(0396)

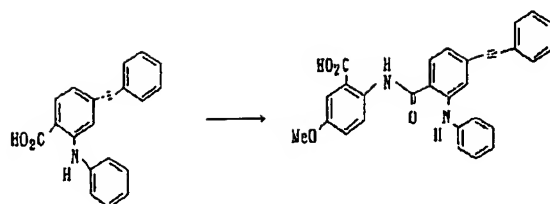
NMR (DMSO-d₆) delta: 7.07 (1H, t, J = 7 Hz), 7.14 (1H, dd, J = 8 Hz, 1 Hz), 7.25-7.29 (2H, m), 7.35-7.46 (6H, m), 7.50-7.60 (4H, m), 7.62-7.68 (1H, m), 7.87 (1H, d, J = 8 Hz), 7.94 (1H, d, J = 8 Hz), 8.07 (1H, d, J = 8 Hz), 8.75 (1H, s), 9.04 (1H, s), 9.47 (1H, s), 12.11 (1H, s), 13.6-14.4 (1H, m).
IR (ν, cm⁻¹, KBr): 3360, 3132, 3056, 1698, 1638, 1548, 1276, 1262, 1194, 754, 692.
EI-MS (m/z, %): 482 (m +, 17), 464 (6), 446 (15), 295 (32), 278 (13), 91 (100).
mp: 264 degrees (dec.).

(0397)

Example 56

5-methoxy-2-(2-phenylamino-4-phenylethynyl benzamide) benzoic acid.

(0398)



(0399)

To methylene chloride (25 ml) solution of 2-phenylamino-4-phenylethynyl benzoic acid 500 mg (1.60 mmol), thionyl chloride 0.14 ml (1.92 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To toluene (50 ml) solution of the residue, 2-amino-5-methoxybenzoic acid 379 mg (2.27 mmol) and potassium carbonate 265 mg (1.92 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and title compound 436 mg (yield 59.0 %) were obtained.

(0400)

NMR (DMSO-d₆) delta: 7.06 (1H, t, J = 7 Hz), 7.10 (1H, dd, J = 8 Hz, 1 Hz), 7.21-7.28 (3H, m), 7.33-7.39 (3H, m), 7.41-7.46 (3H, m), 7.50 (1H, d, J = 3 Hz), 7.54-7.59 (2H, m), 7.80 (1H, d, J = 8 Hz), 8.40 (1H, d, J = 9 Hz), 9.39 (1H, s), 11.66 (1H, s).

IR (ν, cm⁻¹, KBr): 3348, 1700, 1684, 1636, 1610, 1598, 1536, 1496, 1416, 1324, 1286, 1222, 1176, 1042, 830, 750.

El-MS (m/z, %): 462 (m +, 84), 444 (26), 426 (7), 296 (90), 295 (100), 267 (14), 167 (34).

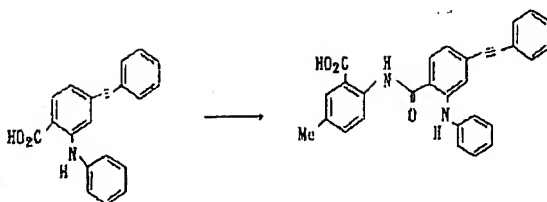
mp: 234-235 degrees.

(0401)

Example 57

5-methyl-2-(2-phenylamino-4-phenylethynyl benzamide) benzoic acid.

(0402)



(0403)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 300 mg (0.96 mmol), thionyl chloride 0.08 ml (1.1 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To toluene (50 ml) solution of the residue, 2-amino-5-methylbenzoic acid 174 mg (1.15 mmol) and potassium carbonate 159 mg (1.15 mmol) were added, and the mixture was heated under reflux for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and it was obtained title compound 375 mg (yield 88.0 %).

(0404)

NMR (DMSO-d₆) delta: 2.33 (3H, s), 7.06 (1H, t, J = 7 Hz), 7.10 (1H, dd, J = 8 Hz, 1 Hz), 7.24 (2H, dd, J = 8 Hz, 1 Hz), 7.33-7.45 (6H, m), 7.47 (1H, dd, J = 8 Hz, 1 Hz), 7.54-7.60 (2H, m) 7.80 (1H, d, J = 8 Hz), 7.85 (1H, d, J = 2 Hz), 8.46 (1H, d, J = 8 Hz), 9.39 (1H, s), 11.95 (1H, s) 13.5-13.9 (1H, m).

IR (ν, cm⁻¹, KBr): 3228, 2212, 1698, 1640, 1596, 1582, 1536, 1496, 1416, 1322, 1290, 1256, 1224, 1176, 1060, 750.

EI-MS (m/z, %): 446 (m +, 7), 428 (2), 295 (10), 267 (2).

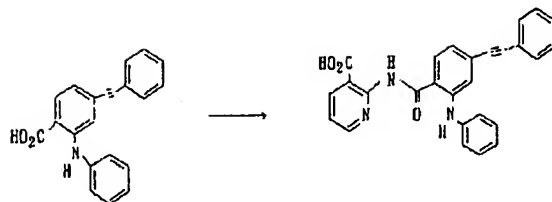
mp: 248-250 degrees.

(0405)

Example 58

2-(2-phenylamino-4-phenyl-ethynyl benzamide) nicotinic acid.

(0406)



(0407)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 300 mg (0.96 mmol), thionyl chloride 0.08 ml (1.1 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-amino nicotinic acid 145 mg (1.05 mmol) and triethylamine 1 ml were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and it was obtained title compound 124 mg (yield 30.0 %).

(0408)

NMR (DMSO-d₆) delta: 7.04-7.10 (2H, m), 7.21-7.25 (2H, m), 7.32-7.46 (7H, m) 7.55-7.60 (2H, m), 7.88 (1H, d, J = 8 Hz), 8.26 (1H, dd, J = 8 Hz, 1 Hz), 8.59 (1H, dd, J = 5.2 Hz), 9.20-9.40 (1H, m), 11.40-11.60 (1H, m).

IR (ν, cm⁻¹, KBr): 3444, 3256, 3100-2900, 2212, 1756, 1664, 1640, 1594, 1554, 1518, 1496, 1444, 1412, 1316, 1272, 1258, 1244, 1210, 770, 752.

FAB-MS (m/z, %): 434 (M + H, 17), 296 (100).

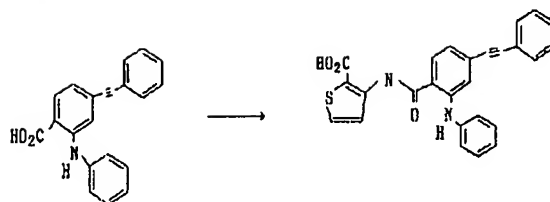
mp: 236-237 degrees.

(0409)

Example 59

3-(2-phenylamino-4-phenyl-ethynyl benzamide) thiophencarboxylic acid.

(0410)



(0411)

To methylene chloride (15 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 250 mg (0.8 mmol), thionyl chloride 0.08 ml (1.0 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 3-amino-2-thiophenecarboxylic acid methyl ester 151 mg (0.96 mmol) and potassium carbonate 133 mg (0.96 mmol) were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography. Obtained ester was dissolved in ethanol (25 ml) and 1M-sodium hydroxide solution 1.4 ml were added and were heated under reflux for four hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. The residue was acidified with hydrochloric acid, and next precipitate was filtered, and it was recrystallised from acetonitrile, and it was obtained title compound 236 mg (yield 78.0 %).

(0412)

NMR (DMSO-d₆) delta: 7.05 (1H, t, J = 7 Hz), 7.15 (1H, dd, J = 8 Hz, 1 Hz), 7.20 (2H, dd, J = 8 Hz, 1 Hz), 7.32-7.46 (6H, m), 7.55-7.60 (2H, m), 7.79 (1H, d, J = 8 Hz), 7.90 (1H, d, J = 5 Hz), 8.08 (1H, d, J = 5 Hz), 9.20 (1H, s), 11.36 (1H, s), 13.5-13.7 (1H, m).

IR (ν, cm⁻¹, KBr): 3392, 3260, 3044, 2636, 2212, 1640, 1608, 1554, 1498, 1446, 1408, 1368, 1258, 1242, 1214, 756.

El-MS (m/z, %): 420 (m +, 41), 296 (100), 278 (75), 256 (38), 205 (55), 178 (46), 147 (46), 133 (54), 129 (62), 121 (58), 119 (48), 115 (50), 108 (70), 105 (69).

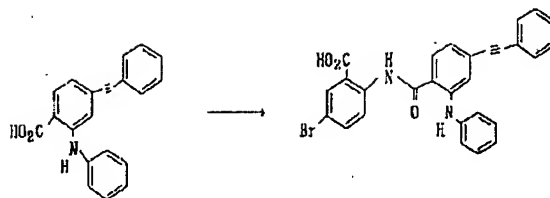
mp: 218-220 degrees.

(0413)

Example 60

5-bromo-2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzoic acid.

(0414)



(0415)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenylethynyl benzoic acid 500 mg (1.60 mmol), thionyl chloride 0.15 ml (2.00 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-amino-5-bromobenzoic acid 415 mg (1.92 mmol) and potassium carbonate 266 mg (1.92 mmol) were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised from acetonitrile, and it was obtained title compound 455 mg (yield 55.6 %).

(0416)

NMR (DMSO-d₆) delta: 7.06 (1H, t, J = 7 Hz), 7.10 (1H, dd, J = 8 Hz, 1, Hz), 7.23 (2H, dd, J = 8 Hz, 1 Hz), 7.33-7.48 (6H, m), 7.54-7.60 (2H, m), 7.80 (1H, d, J = 8 Hz), 7.84 (1H, dd, J = 9 Hz, 2 Hz) 8.09 (1H, d, J = 2 Hz), 8.52 (1H, d, J = 9 Hz), 9.30 (1H, s), 11.96 (1H, s).

IR (ν, cm⁻¹, KBr): 3220, 2220, 1700, 1688, 1636, 1606, 1596, 1576, 1516, 1496, 1418, 1370, 1322, 1284, 1250, 1220, 1180, 824, 790, 764, 750.

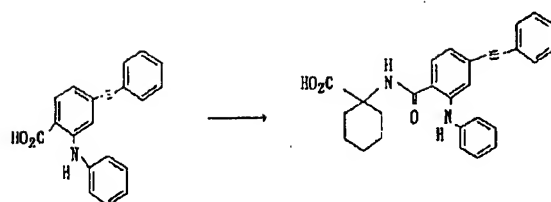
EI-MS (m/z, %): 512 (m +, 10), 494 (4), 295 (30), 267 (7), 239 (1), 190 (1), 163 (1), 91 (2) mp. 261-263 degrees.

(0417)

Example 61

1-(2-phenylamino-4-phenylethynyl benzamide) cyclohexanecarboxylic acid.

(0418)



(0419)

To methylene chloride (20 ml) solution of 2-phenylamino-4-phenyl-ethynyl benzoic acid 500 mg (1.6 mmol), thionyl chloride 0.15 ml (2 mmol) was added, and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 1,1-aminocyclohexanecarboxylic acid benzyl 448 mg (1.92 mmol) and potassium carbonate 266 mg (1.92 mmol) were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with acetonitrile. Obtained crystals were dissolved in ethanol (10 ml) and 1M-sodium hydroxide solution 2 ml were added and were heated under reflux for five hours, and thereafter, ethanol was eliminated by distillation under reduced pressure. The residue was acidified with hydrochloric acid, and next precipitate was filtered, and it was recrystallised from ether, and it was obtained title compound 434 mg (yield 62.0 %).

(0420)

NMR (DMSO-d₆) delta: 1.22-1.35 (1H, m), 1.43-1.62 (5H, m), 1.68-1.82 (2H, m), 2.03-2.18 (2H, m), 7.01-7.07 (2H, m), 7.18 (2H, dd, J = 8 Hz, 1 Hz), 7.31-7.45 (6H, m), 7.54-7.59 (2H, m), 7.73 (1H, d, J = 8 Hz, Hz), 8.52 (1H, s), 9.27 (1H, s), 12.27 (1H, s).

IR (ν, cm⁻¹, KBr): 3432, 3396, 3236, 3040, 2932, 2860, 2624, 2208, 1718, 1634, 1590, 1558, 1516, 1496, 1418, 1270, 1172, 868, 782, 758.

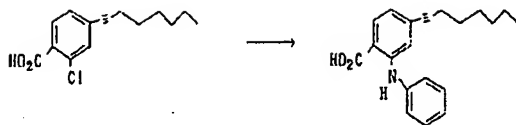
EI-MS (m/z, %): 438 (m +, 49), 420 (8), 394 (3), 349 (14), 295 (100), 267 (14), 239 (3), 163 (3), 98 (6), 81 (3) mp. 194-195 degrees.

(0421)

Reference Example 39

4-(octan-1-yl)-2-phenylamino benzoic acid.

(0422)



(0423)

To aniline (20 ml) solution of 2-chloro-4-(octan-1-yl) benzoic acid 1.95 g (7.36 mmol) were added potassium carbonate 1.22 g (8.83 mmol) and 5 wt.% activated copper and it was heated under reflux for three hours, and aniline was eliminated by distillation under reduced pressure. The residue was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with methylene chloride, and it was recrystallised from methanol, and title compound 2.12 g (yield 90.0 %) were obtained.

(0424)

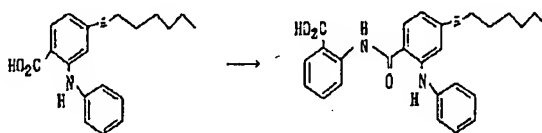
NMR (CDCl₃) delta: 0.89 (3H, t, J = 7 Hz), 1.23-1.43 (6H, m), 1.57 (2H, q, J = 7 Hz) 2.37 (2H, t, J = 7 Hz), 6.75 (1H, dd, J = 8 Hz, 1 Hz), 7.15 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.21 (1H, d, J = 1 Hz), 7.24-7.29 (2H, m), 7.35-7.42 (2H, m), 7.93 (1H, d, J = 8 Hz), 9.28 (1H, s).

(0425)

Example 62

2-(4-(octan-1-yl)-2-phenylamino phenylamino benzamide) benzoic acid.

(0426)



(0427)

To methylene chloride (20 ml) solution of 4-(octan-1-yl)-2-phenylamino benzoic acid 520 mg (1.62 mmol) produced in Reference Example 39 was added thionyl chloride 0.12 ml (1.62 mmol), and it was stirred at room temperature for three hours, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue were added 2-

aminobenzoic acid 267 mg (1.94 mmol) and potassium carbonate 268 mg (1.94 mmol) and triethylamine 0.27 ml (1.94 mmol), and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 450 mg (yield 63 %) were obtained.

(0428)

NMR (CDCl₃) delta: 0.88 (3H, t, J = 7 Hz), 1.20-1.44 (10H, m), 1.50-1.60 (2H, m) 2.38 (2H, t, J = 7 Hz), 6.87 (1H, dd, J = 7.1 Hz), 7.07 (1H, t, J = 7 Hz), 7.14-7.20 (1H, m), 7.23-7.30 (2H, m), 7.32-7.39 (3H, m), 7.64-7.70 (2H, m), 8.15-8.21 (1H, m), 8.83 (1H, dd, J = 8 Hz, 1 Hz), 9.61 (1H, s), 11.69 (1H, s).

IR (ν, cm⁻¹, KBr): 3300, 3044, 2228, 1682, 1652, 1606, 1580, 1562, 1542, 1516, 1498, 1470, 1452, 1420, 1320, 1294, 1258, 1224, 1160, 1068, 1028, 870, 752.

EI-MS (m/z, %): 440 (m +, 100), 422 (24), 303 (59), 260 (20), 246 (20), 233 (31), 204 (23).

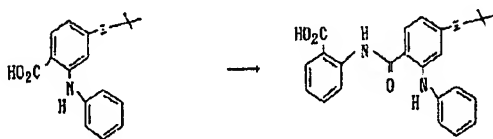
mp: 165-167 degrees.

(0429)

Example 63

2-(4-(3,3-dimethyl butenyl)-2-phenylamino benzamide) benzoic acid.

(0430)



(0431)

To methylene chloride (20 ml) solution of 4-(3,3-dimethyl butenyl)-2-phenylamino benzoic acid 587 mg (2.00 mmol) was added thionyl chloride 0.2 ml (2.67 mmol), and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-aminobenzoic acid 302 mg (2.20 mmol), potassium carbonate 304 mg (2.20 mmol) and triethylamine 0.30 ml (2.20 mmol) were added, and the mixture was stirred at room temperature for 18 hours. The reaction solution was

acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from acetonitrile, and title compound 654 mg (yield 79.0 %) were obtained.

(0432)

NMR (CDCl₃) delta: 1.30 (9H, s), 6.87 (1H, dd, J = 8 Hz, 1 Hz), 7.04-7.10 (1H, m), 7.14-7.20 (1H, m), 7.23-7.29 (2H, m), 7.32-7.39 (3H, m), 7.63-7.70 (2H, m), 8.19 (1H, dd, J = 8 Hz, 1 Hz), 8.82 (1H, dd, J = 8 Hz, 1 Hz), 9.60 (1H, s), 11.67 (1H, s).

IR (ν, cm⁻¹, KBr): 3288, 2972, 2224, 1656, 1608, 1582, 1560, 1532, 1498, 1420, 1294, 1256, 1224, 1162, 900, 764, 752.

EI-MS (m/z, %): 412 (m+, 44), 394 (6), 295 (2), 275 (76), 260 (38), 246 (5).

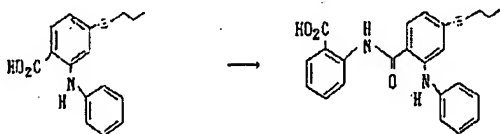
mp: 225-227 degrees.

(0433)

Example 64

2-(2-phenylamino-4-(pentan-1-yl) benzamide) benzoic acid.

(0434)



(0435)

To methylene chloride (25 ml) solution of 2-phenylamino-4-(pentan-1-yl) benzoic acid 510 mg (1.83 mmol) was added thionyl chloride 0.14 ml (1.83 mmol), and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-aminobenzoic acid 302 mg (2.20 mmol), potassium carbonate 304 mg (2.20 mmol) and triethylamine 0.30 ml (2.20 mmol) were added, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by

distillation under reduced pressure. The residue was purified by recrystallisation from acetonitrile, and title compound 530 mg (yield 73.0 %) were obtained.

(0436)

NMR (CDCl₃) delta: 1.03 (3H, t, J = 7 Hz) 1.50-1.65 (2H, m), 2.37 (2H, t, J = 7.1 Hz), 6.88 (1H, dd, J = 1.5 Hz, 8.3 Hz), 7.07 (1H, ddd, J = 7 Hz, 7 Hz, 1 Hz), 7.14-7.21 (1H, m), 7.23-7.30 (2H, m), 7.32-7.40 (3H, m), 7.63-7.71 (2H, m), 8.19 (1H, dd, J = 8 Hz, 1 Hz), 8.83 (1H, dd, J = 8 Hz, 1 Hz), 9.60 (1H, s), 11.67 (1H, s).

IR (ν, cm⁻¹, KBr): 3256, 3020, 2872, 2224, 1656, 1606, 1582, 1562, 1534, 1498, 1470, 1452, 1420, 1318, 1258, 1222, 1162, 892, 758,.

EI-MS (m/z, %): 398 (m +, 45 %), 380 (6), 261 (54), 233 (17), 204 (11), 190 (2), 146 (2), 119 (3).

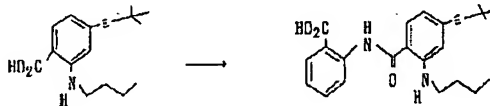
mp: 199-200 degrees.

(0437)

Example 65

2-(2-butylamino-4-(3,3-dimethyl butenyl) benzamide) benzoic acid.

(0438)



(0439)

To methylene chloride (15 ml) solution of 2-butylamino-4-(3,3-dimethyl butenyl) benzoic acid 547 mg (2.00 mmol) was added thionyl chloride 0.2 ml (2.67 mmol), and it was stirred at room temperature for one hour 30 minutes, and next the solvent was eliminated by distillation under reduced pressure. To methylene chloride (50 ml) solution of the residue, 2-aminobenzoic acid 302 mg (2.20 mmol), potassium carbonate 304 mg (2.20 mmol) and triethylamine 0.30 ml (2.20 mmol) were added, and the mixture was stirred at room temperature for 16 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next the organic layer was separated and recovered. The organic layer was washed successively with 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from acetonitrile, and title compound 659 mg (yield 84.0 %) were obtained.

(0440)

NMR (CDCl₃) delta: 0.97 (3H, t, J = 7 Hz), 1.34 (9H, s), 1.42-1.53 (2H, m), 1.65-1.73 (2H, m), 3.16-3.20 (2H, m), 6.69 (1H, dd, J = 8 Hz, 2 Hz), 6.74 (1H, d, J = 2 Hz), 7.14 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.59 (1H, d, J = 8 Hz), 7.63 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 8.17 (1H, dd, J = 8 Hz, 1 Hz), 8.78 (1H, dd, J = 8 Hz, 1 Hz).

IR (ν, cm⁻¹, KBr): 3332, 3072, 2964, 2228, 1650, 1608, 1536, 1220, 766, 754.

FAB-MS (m/z, %): 391(M-H).

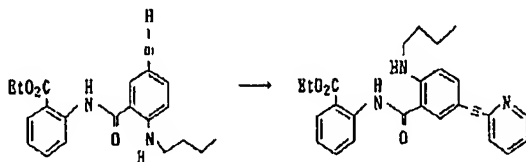
mp: 225-227 degrees.

(0441)

Reference Example 40

2-(2-butylamino-5-(2-pyridyl ethynyl) benzamide) benzoic acid ethyl ester.

(0442)



(0443)

2-iodopyridine 0.30 ml (2.89 mmol), dichlorobis triphenylphosphine palladium 16 mg (0.01 mmol) and copper iodide 10 mg (0.03 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 526 mg (1.44 mmol), and the mixture was stirred at room temperature for two hours. Water was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water, saturated aqueous potassium hydrogen sulphate solution, 10 % sodium thiosulfate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 375 mg (yield 77.5 %) were obtained.

(0444)

NMR (CDCl₃) delta: 0.97 (3H, t, J = 7 Hz), 1.42 (3H, t, J = 7 Hz), 1.40-1.50 (2H, m), 1.64-1.71 (2H, m), 3.18-3.24 (2H, m), 4.43 (2H, q, J = 7 Hz), 7.12 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.19 (1H, ddd, J = 8 Hz, 5, 1 Hz), 7.50 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.55-7.61 (2H, m), 7.66 (1H, ddd, J = 8 Hz, 8

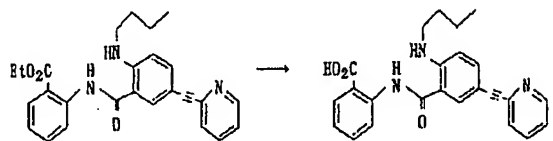
Hz, 2 Hz), 7.97 (1H, d, J = 2 Hz), 8.06 (1H, t, J = 5 Hz), 8.10 (1H, dd, J = 8 Hz, 2 Hz), 8.58-8.61 (1H, m), 8.66 (1H, dd, J = 8 Hz, 1 Hz), 11.77 (1H, s).

(0445)

Example 66

2-(2-butylamino-5-(2-pyridyl ethynyl) benzamide) benzoic acid.

(0446)



(0447)

1M-sodium hydroxide solution 1 ml was added to ethanol (20 ml) solution of 2-(2-butylamino-5-(2-pyridyl ethynyl) benzamide) benzoic acid ethyl ester 375 mg (0.85 mmol) produced in Reference Example 40 and it was heated under reflux for two hours and thereafter, it was cooled to room temperature. The reaction solution was neutralised with saturated potassium hydrogensulfate, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 194 mg (yield 55.0 %) were obtained.

(0448)

NMR (DMSO-d₆) delta: 0.94 (3H, t, J = 7 Hz), 1.36-1.46 (2H, m), 1.57-1.65 (2H, m), 3.21-3.26 (2H, m), 6.86 (1H, d, J = 9 Hz), 7.19-7.24 (1H, m), 7.37 (1H, ddd, J = 8 Hz, 5,1 Hz), 7.56-7.60 (2H, m), 7.65 (1H, ddd, J = 8 Hz, 7 Hz, 2 Hz), 7.83 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.96 (1H, d, J = 2 Hz), 8.04 (1H, dd, J = 8 Hz, 2 Hz), 8.18 (1H, t, J = 5 Hz), 8.54 (1H, dd, J = 8 Hz, 1 Hz), 8.57-8.60 (1H, m), 12.03 (1H, s).

IR (ν, cm⁻¹, KBr): 2204, 1652, 1590, 1528, 1220, 770, 756.

FAB-MS (m/z, %): 412 (M-H, 100).

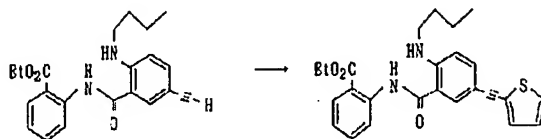
mp: 179-180 degrees.

(0449)

Reference Example 41

2-(2-butylamino-5-(2-thiophenyl ethynyl) benzamide) benzoic acid ethyl ester.

(0450)



(0451)

2-iodo thiophene 0.30 ml (2.89 mmol), dichlorobis triphenylphosphine palladium 16 mg (0.01 mmol) and copper iodide 10 mg (0.03 mmol) were added to diethylamine (10 ml) solution of 2-(2-butylamino-5-ethynyl benzamide) benzoic acid ethyl ester 500 mg (1.37 mmol) produced in Reference Example 30, and the mixture was stirred at room temperature for two hours. Water was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water, saturated aqueous potassium hydrogen sulphate solution, 10 % sodium thiosulfate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 233 mg (yield 38.0 %) were obtained.

(0452)

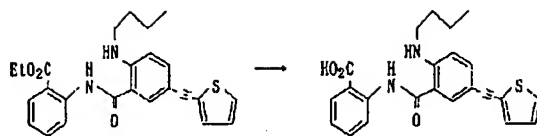
NMR (CDCl₃) delta: 0.97 (3H, t, J = 7 Hz), 1.43 (3H, t, J = 7 Hz), 1.41-1.52 (2H, m), 1.64-1.73 (2H, m), 3.18-3.22 (2H, m), 4.43 (2H, q, J = 7 Hz), 6.69 (1H, d, J = 9 Hz), 7.00 (1H, dd, J = 5.4 Hz), 7.12 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.23-7.26 (2H, m), 7.47 (1H, dd, J = 8 Hz, 1 Hz), 7.58 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 7.89 (1H, J = 2 Hz), 8.03 (1H, t, J = 5 Hz), 8.10 (1H, dd, J = 8 Hz, 1 Hz), 8.67 (1H, dd, J = 8 Hz, 1 Hz).

(0453)

Example 67

2-(2-butylamino-5-(2-thiophenyl ethynyl) benzamide) benzoic acid.

(0454)



(0455)

1M-sodium hydroxide solution 1 ml was added to ethanol (20 ml) solution of 2-(2-butylamino-5-(2-thiophenyl ethynyl) benzamide) benzoic acid ethyl ester 230 mg (0.52 mmol) produced in Reference Example 41 and was heated under reflux for three hours and thereafter, it was cooled to room temperature. The reaction solution was neutralised with saturated potassium hydrogensulfate, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 185 mg (yield 85.0 %) were obtained.

(0456)

NMR (DMSO-d₆) delta: 0.94 (3H, t, J = 7 Hz), 1.36-1.46 (2H, m), 1.56-1.64 (2H, m), 3.19-3.25 (2H, m), 6.83 (1H, d, J = 9 Hz), 7.11 (1H, dd, J = 5 Hz, 4 Hz), 7.18-7.24 (1H, m), 7.35 (1H, dd, J = 4 Hz, 1 Hz), 7.52 (1H, dd, J = 9 Hz, 2 Hz), 7.60-7.67 (2H, m), 7.88 (1H, d, J = 2 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.11 (1H, dd, J = 8 Hz, 1 Hz), 8.51 (1H, dd, J = 8 Hz, 1 Hz), 11.97 (1H, s).

IR (ν, cm⁻¹, KBr): 3320, 2964, 2208, 1652, 1602, 1530, 1254, 756.

FAB-MS (m/z, %): 417 (M-H, 16), 189 (100)

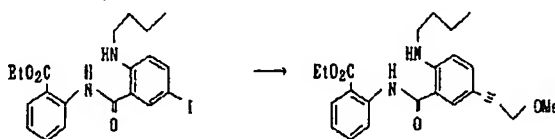
mp. 79-180 degrees.

(0457)

Reference Example 42

2-(2-butylamino-5-(3-methoxy propan-1-yl) benzamide) benzoic acid ethyl ester.

(0458)



(0459)

3-methoxy-1-propine 0.25 ml (3.00 mmol), dichlorobis triphenylphosphine palladium 53 mg (0.08 mmol) and copper iodide 14 mg (0.08 mmol) were added to mixed solution of 10 ml of tetrahydrofuran and 20 ml of diethylamine containing 2-(2-butylamino-5-iodo benzamide) benzoic acid ethyl ester 700 mg (1.50 mmol) produced in Reference Example 30 and were stirred at room temperature for two hours. Water was added, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated potassium hydrogensulfate solution, 10 % sodium thiosulfate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol, and title compound 375 mg (yield 61.2 %) were obtained.

(0460)

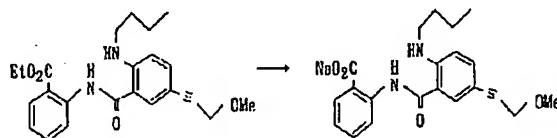
NMR (CDCl₃) delta: 0.96 (3H, t, J = 7 Hz), 1.40-1.51 (5H, m), 1.62-1.71 (2H, m), 3.16-3.22 (2H, m), 3.47 (3H, s), 4.20 (2H, q, J = 7 Hz), 4.34 (2H, s), 7.11 (1H, ddd, J = 8.7, 1 Hz), 7.41 (1H, dd, J = 8 Hz, 2 Hz), 7.57 (1H, ddd, J = 8.7, 1 Hz), 7.84 (1H, d, J = 2 Hz), 8.00 (1H, t, J = 5 Hz), 8.09 (1H, dd, J = 8.1 Hz), 8.68 (1H, dd, J = 8.1 Hz), 11.75 (1H, s).

(0461)

Example 68

2-(2-butylamino-5-(3-methoxy propan-1-yl) benzamide) sodium benzoate salt.

(0462)



(0463)

1M-sodium hydroxide solution 2 ml were added to mixed solution of 20 ml of tetrahydrofuran and 20 ml of ethanol containing 2-(2-butylamino-5-(3-methoxy propan-1-yl) benzamide) benzoic acid ethyl ester 370 mg (0.91 mmol) produced in Reference Example 42, and the mixture was stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol-ether-hexane, and title compound 300 mg (yield 85.9 %) were obtained.

(0464)

NMR (DMSO-d₆) delta: 0.93 (3H, t, J = 7 Hz), 1.36-1.46 (2H, m), 1.55-1.64 (2H, m), 3.15-3.21 (2H, m), 4.31 (2H, s), 6.73 (1H, d, J = 9 Hz), 6.96-7.01 (1H, m), 7.28-7.33 (1H, m), 7.39 (1H, dd, J = 9 Hz, 2 Hz), 7.90 (1H, d, J = 2 Hz), 8.03 (1H, dd, J = 8 Hz, 1 Hz), 8.37 (1H, t, J = 5 Hz), 8.54 (1H, d, J = 8 Hz).

IR (ν, cm⁻¹, KBr): 3300, 2956, 2928, 2212, 1652, 1590, 1522, 1296, 760.

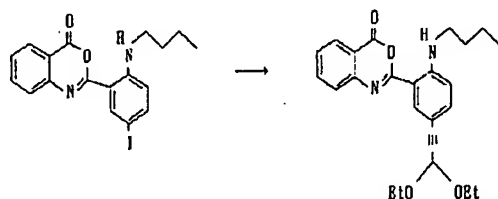
FAB-MS (m/z, %): 424 (m + Na, 100) mp. 179-180 degrees.

(0465)

Reference Example 43

2-(2-butylamino-5-(3,3-diethoxy propan-1-yl) phenyl)-4-oxo-4H-3,1-benzoxazine

(0466)



(0467)

Propargyl aldehyde diethyl acetal 0.96 ml (1.72 mmol), dichlorobis triphenylphosphine palladium 30 mg (0.03 mmol) and copper iodide 20 mg (0.06 mmol) were added to triethylamine (30 ml) and tetrahydrofuran (15 ml) solution of 2-(2-butylamino-5-iodo phenyl)-4-oxo-4H-3,1-benzoxazine 1.40 g (3.33 mmol), and under a nitrogen atmosphere, it was stirred at room temperature for one hour. Water was added to the reaction solution, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water, saturated aqueous potassium hydrogen sulphate solution, 10 % sodium thiosulfate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from acetonitrile, and title compound 625 mg (yield 41.4 %) were obtained.

(0468)

NMR (CDCl₃) delta: 1.04 (3H, t, J = 7 Hz), 1.29 (6H, t, J = 7 Hz), 1.53-1.63 (2H, m), 1.75-1.84 (2H, m), 3.29-3.34 (2H, m), 3.63-3.72 (2H, m), 3.80-3.89 (2H, m), 5.50 (1H, s), 6.68 (1H, d, J = 9 Hz),

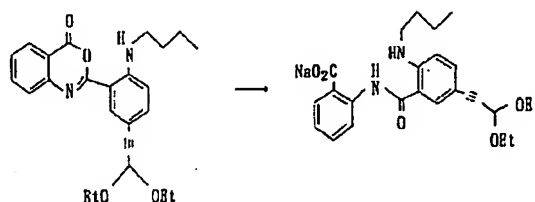
7.43-7.52 (3H, m), 7.80 (1H, ddd, J = 8 Hz, 7 Hz, 1 Hz), 8.22 (1H, ddd, J = 8 Hz, 1,1 Hz), 8.32 (1H, d, J = 2 Hz), 9.25 (1H, t, J = 5 Hz).

(0469)

Example 69

2-(2-butylamino-5-(3,3-diethoxy propan-1-yl) benzamide) sodium benzoate salt.

(0470)



(0471)

1M-sodium hydroxide solution 5 ml were added to mixed solution of 20 ml of tetrahydrofuran and 20 ml of ethanol containing 2-(2-butylamino-5-(3,3-diethoxy propan-1-yl) phenyl)-4-oxo-4H-3,1-benzoxazine 600 mg (1.43 mmol) produced in Reference Example 43, and the mixture was stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by recrystallisation from methanol-ether-hexane, and title compound 580 mg (yield 88.0 %) were obtained.

(0472)

NMR (CDCl₃) delta: 0.93 (3H, t, J = 7 Hz), 1.18 (6H, t, J = 7 Hz), 1.38-1.46 (2H, m), 1.55-1.64 (2H, m), 3.16-3.21 (2H, m), 3.53-3.61 (2H, m), 3.65-3.73 (2H, m), 5.50 (1H, s), 6.75 (1H, d, J = 9 Hz), 6.98-7.03 (1H, m), 7.31-7.36 (1H, m), 7.40 (1H, dd, J = 9 Hz, 2 Hz), 7.89 (1H, d, J = 2 Hz), 8.06-8.09 (1H, m), 8.39 (1H, t, J = 5 Hz), 8.55 (1H, dd, J = 8 Hz, 1 Hz).

IR (ν, cm⁻¹, KBr): 2960, 2932, 2220, 1660, 1594, 1520, 1288, 754.

FAB-MS (m/z, %): 437 (M-H, 34), 379 (100).

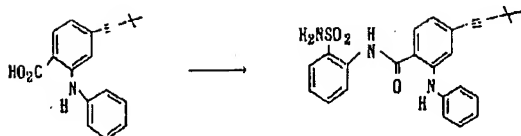
mp: 179-180 degrees.

(0473)

Example 70

4-(3,3-dimethyl butenyl)-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide.

(0474)



(0475)

4-(3,3-dimethyl butenyl)-2-phenylamino benzoic acid 1.0 g (3.40 mmol) and methylene chloride (30 ml) solution of thionyl chloride 0.4 ml were stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (30 ml) solution of the residue was dropwise-added under ice cooling to pyridine (50 ml) solution of 2-aminobenzene sulfonamide 0.65 g (3.75 mmol), and it was stirred at room temperature for 18 hours, and next methylene chloride was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1 M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.8 g (yield 52.0 %) were obtained.

(0476)

NMR (CDCl₃) delta: 1.29 (9H, s), 4.87 (2H, br-s), 6.85 (1H, dd, J = 8 Hz, 2 Hz), 7.09 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.21-7.29 (3H, m), 7.52-7.59 (2H, m), 7.57 (1H, d, J = 8 Hz), 7.63 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.99 (1H, dd, J = 8 Hz, 2 Hz), 8.41 (1H, dd, J = 8 Hz, 1 Hz), 9.53 (1H, s), 10.03 (1H, s).

IR (v, cm⁻¹, KBr): 3364, 2972, 2928, 2224, 1642, 1586, 1556, 1516, 1500, 1472, 1442, 1420, 1334, 1290, 1272, 1222, 1154, 764.

FAB-MS (m/z, %): 446 (M-H, 100).

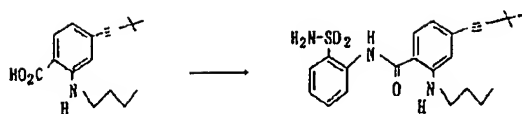
mp: 101-102 degrees.

(0477)

Example 71

2-butylamino-4-(3,3-dimethyl butenyl)-N-(2-sulphamoyl phenyl) benzamide.

(0478)



(0479)

2-butylamino-4-(3,3-dimethyl butenyl) benzoic acid 1.0 g (3.66 mmol) and methylene chloride (30 ml) solution of thionyl chloride 0.4 ml were stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (30 ml) solution of the residue was dropwise-added under ice cooling to pyridine (50 ml) solution of 2-aminobenzene sulfonamide 0.7 g (4.03 mmol), and it was stirred at room temperature for 18 hours, and next methylene chloride was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1 M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.9 g (yield 54.0 %) were obtained.

(0480)

NMR (DMSO-d₆) delta: 0.97 (3H, t, J = 7 Hz), 1.34 (9H, s), 1.41-1.51 (2H, m), 1.62-1.72 (2H, m), 3.18 (2H, t, J = 7 Hz), 4.83 (2H, br-s), 6.45 (1H, dd, J = 8.2 Hz), 6.74 (1H, d, J = 2 Hz), 7.23 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.48 (1H, d, J = 8 Hz), 7.61 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.86 (1H, br-s), 7.95 (1H, dd, J = 8 Hz, 2 Hz), 8.34 (1H, dd, J = 8 Hz, 1 Hz), 9.70 (1H, s).

IR (ν, cm⁻¹, KBr): 3368, 3232, 3084, 2968, 2932, 2868, 2224, 1644, 1600, 1584, 1564, 1530, 1472, 1440, 1342, 1292, 1226, 1168, 1156, 896, 764.

FAB-MS (m/z, %): 426 (M-H, 100).

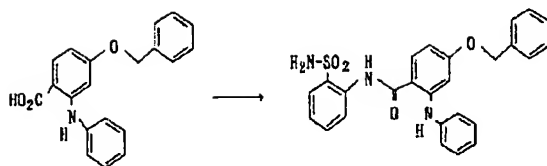
mp: 130-131 degrees.

(0481)

Example 72

4-benzyloxy-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide.

(0482)



(0483)

To methylene chloride (15 ml) solution of 4-benzyloxy-2-phenylamino benzoic acid 500 mg (1.56 mmol) was added thionyl chloride 186 mg (1.56 mmol) under ice cooling, and it was stirred at room temperature for two hours. This solution was dropwise-added to 2-aminobenzene sulfonamide 174 mg (0.96 mmol) and methylene chloride (15 ml) solution of triethylamine 1 ml (7.8 mmol) and was stirred at room temperature for four hours. To the reaction solution, water was added, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, water, 1M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography and recrystallisation from ethanol, and title compound 210 mg (yield 28.0 %) were obtained.

(0484)

NMR (delta, DMSO-d₆): 4.82 (2H, s), 5.04 (2H, s), 6.48 (1H, dd, J = 9 Hz, 2 Hz), 6.85 (1H, d, J = 2 Hz), 7.04-7.10 (1H, m), 7.15 (2H, dd, J = 9 Hz, 2 Hz), 7.22-7.41 (8H, m), 7.60-7.65 (2H, m), 7.98 (1H, dd, J = 8 Hz, 1 Hz), 8.38 (1H, dd, J = 8 Hz, 1 Hz), 9.74 (1H, s), 9.87 (1H, s).

IR (ν, cm⁻¹, KBr): 1646, 1580, 1522, 1286, 756.

EI-MS (m/z, %): 473 (31), 446 (10), 302 (18), 301 (30), 300(11), 91 (100).

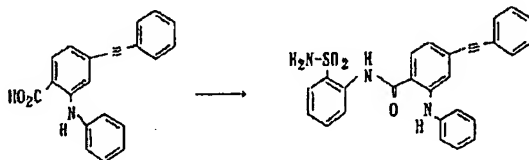
mp: 171-172 degrees.

(0485)

Example 73

4-phenyl-ethynyl-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide.

(0486)



(0487)

2-phenylamino-4-phenyl-ethynyl benzoic acid 1 g (3.40 mmol) and methylene chloride (30 ml) solution of thionyl chloride 0.4 ml were stirred at room temperature for two hours, and next the solvent was eliminated by distillation under reduced pressure. Methylene chloride (30 ml) solution of the residue was dropwise-added under ice cooling to pyridine (50 ml) solution of 2-aminobenzene sulfonamide 0.65 g (3.75 mmol), and it was stirred at room temperature for 18 hours, and next methylene chloride was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1 M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.8 g (yield 52.0 %) were obtained.

(0488)

NMR (CDCl₃) delta: 1.29 (9H, s), 4.87 (2H, br-s), 6.85 (1H, ddd, J = 8 Hz, 2 Hz, 1 Hz), 7.09 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.21-7.29 (3H, m), 7.52-7.59 (2H, m), 7.57 (1H, d, J = 8 Hz), 7.63 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.99 (1H, dd, J = 8 Hz, 2 Hz), 8.41 (1H, dd, J = 8 Hz, 1 Hz), 9.53 (1H, s), 10.03 (1H, s).

IR (ν, cm⁻¹, KBr): 3380, 3320, 3244, 3056, 2212, 1644, 1594, 1582, 1558, 1530, 1500, 1468, 1442, 1424, 1334, 1294, 1226, 1154, 756.

EI-MS (m/z, %): 467 (m +, 59), 295 (100), 267 (16).

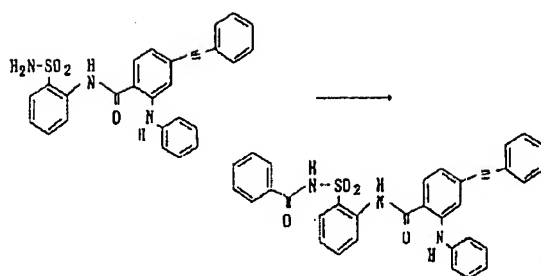
mp: 195-196 degrees.

(0489)

Example 74

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl) benzamide.

(0490)



(0491)

To mixed solution of 10 ml of water and 10 ml dioxane, benzoyl chloride 90 mg (0.64 mmol) were dropwise-added, and potassium carbonate 118 mg (0.86 mmol) were stirred at room temperature 4-phenyl-ethynyl-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 200 mg (0.43 mmol) produced in Example 73 for 16 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with methanol, and title compound 168 mg (yield 69.0 %) were obtained.

(0492)

NMR (CDCl₃) delta: 7.00 (1H, dd, J = 8 Hz, 1 Hz), 7.07-7.12 (1H, m), 7.27-7.77 (16H, m), 7.92 (1H, d, J = 8 Hz), 8.07 (1H, dd, J = 8 Hz, 1 Hz), 8.62 (1H, dd, J = 8 Hz, 1 Hz), 8.70 (1H, s), 9.60 (1H, s), 10.49 (1H, s).

IR (ν, cm⁻¹, KBr): 3384, 3326, 1704, 1660, 1596, 1582, 1562, 1520, 1286, 752.

FAB-MS (m/z, %): 570 (M-H, 100)

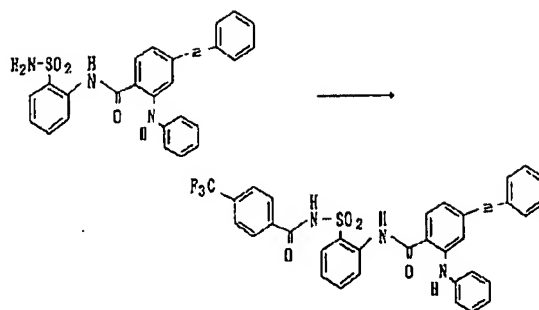
mp. 241-243 degrees.

(0493)

Example 75

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl)-4-trifluoromethyl benzamide.

(0494)



(0495)

To mixed solution of 10 ml water and 10 ml dioxane containing potassium carbonate 118 mg (0.856 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 200 mg (0.43 mmol) produced in Example 73, was added under a stream of nitrogen 4-trifluoromethyl benzoyl chloride 179 mg (0.856 mmol) and the mixture was stirred at room temperature for 16 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with methanol, and the target substance was obtained 168 mg (yield 61.0 %).

(0496)

NMR (CDCl₃) delta: 7.04-7.10 (2H, m), 7.21-7.25 (2H, m), 7.32-7.46 (7H, m), 7.55-7.60 (2H, m), 7.88 (1H, d, J = 8 Hz), 8.26 (1H, dd, J = 7 Hz, 2 Hz), 8.59 (1H, dd, J = 5 Hz, 2 Hz), 9.2-9.4 (1H, m), 11.4-11.6 (1H, m).

IR (ν, cm⁻¹, KBr): 3320, 3244, 2216, 1706, 1662, 1642, 1594, 1580, 1558, 1528, 1498, 1472, 1442, 1422, 1326, 1288, 1256, 1226, 1156, 1130, 1070, 756.

EI-MS (m/z, %): 639 (m +, 16), 467 (20), 446 (10), 422 (17), 295 (88), 278 (42).

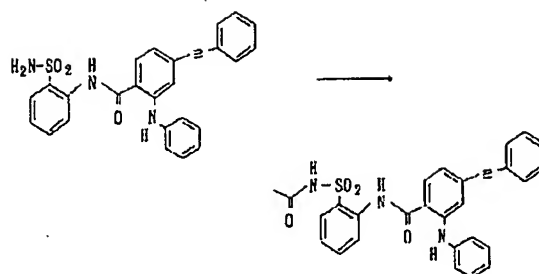
mp: 178-180 degrees.

(0497)

Example 76

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl) acetamide.

(0498)



(0499)

Acetic anhydride 0.12 ml (1.28 mmol) were added under a stream of nitrogen to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 315 mg (2.57 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 400 mg (0.86 mmol) produced in Example 73, and the mixture was stirred at room temperature for two hours. The reaction solution was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography, and title compound 358 mg (yield 82.2 %) were obtained.

(0500)

NMR (CDCl₃) delta: 2.08 (3H, s), 6.99 (1H, dd, J = 8 Hz, 1 Hz), 7.07-7.12 (1H, m), 7.26-7.40 (8H, m), 7.46-7.54 (3H, m), 7.66-7.71 (1H, m), 7.82 (1H, d, J = 8 Hz), 8.01 (1H, dd, J = 8 Hz, 1 Hz), 8.06-8.16 (1H, m), 8.58 (1H, dd, J = 8 Hz, 1 Hz), 9.57 (1H, s), 10.30 (1H, s).

IR (v, cm⁻¹, KBr): 3450-2950, 2864, 2212, 1714, 1660, 1582, 1556, 1530, 1498, 1472, 1442, 1420, 1342, 1318, 1286, 1256, 1224, 1156, 1128, 854, 756.

EI-MS (m/z, %): 509 (m +, 22), 295 (49), 267 (7), 91 (2), 61 (3).

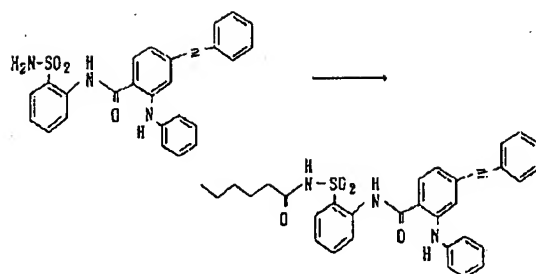
mp: 108 degrees.

(0501)

Example 77

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzenesulphonyl) hexane amide.

(0502)



(0503)

4-dimethylaminopyridine 260 mg (2.14 mmol) and hexanoyl chloride 0.16 ml (1.17 mmol) were added to tetrahydrofuran (10 ml) solution of 4-phenyl-ethynyl-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 500 mg (1.04 mmol) produced in Example 73, and the mixture was stirred at room temperature for one hour. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 200 mg (yield 33.3 %) were obtained.

(0504)

NMR (CDCl₃) delta: 0.84 (3H, t, J = 7 Hz), 1.16-1.32 (4H, m), 1.50-1.62 (2H, m), 2.23 (2H, t, J = 7 Hz), 6.99 (1H, dd, J = 8 Hz, 1 Hz), 7.06-7.12 (1H, m), 7.24-7.30 (3H, m), 7.32-7.40 (5H, m), 7.46-7.54 (3H, m), 7.65-7.71 (1H, m), 7.83 (1H, d, J = 8 Hz), 8.01 (1H, dd, J = 8 Hz, 1 Hz), 8.10 (1H, br-s), 8.57 (1H, dd, J = 8 Hz, 1 Hz), 9.57 (1H, s), 10.31 (1H, s).

IR (ν, cm⁻¹, KBr): 2956, 1714, 1660, 1582, 1442, 1286, 756, 692.

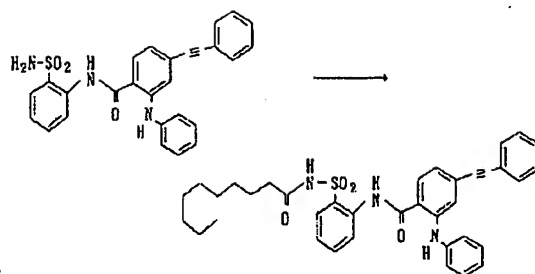
EI-MS (m/z, %): 565 (m+, 41), 467 (4), 295 (100), 267 (13), 205 (29).

(0505)

Example 78

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzenesulphonyl) decane amide.

(0506)



(0507)

Under a stream of nitrogen, decanoyl chloride 153 mg (0.806 mmol) was added to mixed solution of 10 ml water and 10 ml dioxane containing potassium carbonate 148 mg (1.07 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 250 mg (0.54 mmol) produced in Example 73, and the mixture was stirred at room temperature for 20 hours. The reaction solution was acidified with 1M-hydrochloric acid, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride) (and title compound 238 mg (yield 71.5 %) were obtained.

(0508)

NMR (CDCl₃) delta: 0.86 (3H, t, J = 7 Hz), 1.12-1.32 (11H, m), 1.50-1.62 (3H, m), 2.23 (2H, t, J = 7 Hz), 6.99 (1H, dd, J = 8 Hz, 1 Hz), 7.09 (1H, t, J = 7 Hz), 7.24-7.42 (8H, m), 7.47-7.68 (1H, t, J = 7 Hz), 7.83 (1H, d, J = 8 Hz), 8.00 (1H, dd, J = 8 Hz, 1 Hz), 8.08 (1H, s), 8.57 (1H, d, J = 8 Hz), 9.57 (1H, s), 10.32 (1H, s).

IR (ν, cm⁻¹, KBr): 3252, 2928, 2856, 2216, 1714, 1668, 1594, 1578, 1564, 1524, 1500, 1470, 1440, 1418, 1342, 1314, 1286, 1226, 1156, 870, 754, 724, 690, 582.

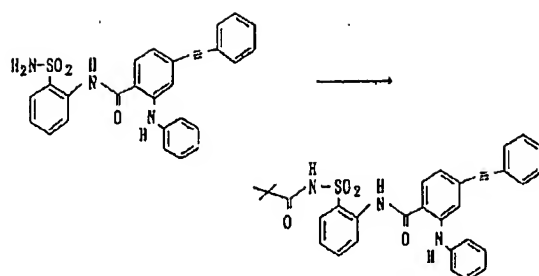
EI-MS (m/z, %): 621 (m +, 50 %), 467 (12), 446 (13), 295 (100), 278 (9), 267 (13).

(0509)

Example 79

N-(2-(2-phenylamino-4-phenyl-ethynyl benzamide) benzensulphonyl) pivalamide.

(0510)



(0511)

Under a stream of nitrogen, pivaloyl chloride 0.07 ml (0.57 mmol) was added to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 118 mg (0.96 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 226 mg (0.48 mmol) produced in Example 73, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with 1 M-hydrochloric acid, water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 150 mg (yield 56.0 %) were obtained.

(0512)

NMR (CDCl₃) delta: 1.14 (9H, s), 7.00 (1H, dd, J = 8 Hz, 2 Hz), 7.09 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.24-7.31 (3H, m), 7.33-7.39 (5H, m), 7.48-7.53 (3H, m), 7.68 (1H, dd, J = 8 Hz, 2 Hz), 7.83 (1H, d, J = 8 Hz), 8.00 (1H, dd, J = 8 Hz, 2 Hz), 8.18 (1H, br-s), 8.53 (1H, dd, J = 8 Hz, 2 Hz), 9.57 (1H, s), 10.25 (1H, s).

IR (ν, cm⁻¹, KBr): 2212, 1704, 1658, 1582, 1558, 1532, 1472, 1442.

EI-MS (m/z, %): 551 (m +, 49), 521 (30), 295 (100), 195 (48).

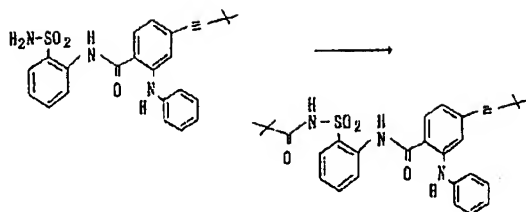
mp: 223-224 degrees.

(0513)

Example 80

N-(2-(4-(3,3-dimethyl butenyl)-2-phenylamino benzamide) benzenesulphonyl) pivalamide.

(0514)



(0515)

Under a stream of nitrogen, pivaloyl chloride 0.06 ml (0.49 mmol) was added to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 110 mg (0.9 mmol) and 4-(3,3-dimethyl butenyl)-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 200 mg (0.45 mmol) produced in Example 70, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 180 mg (yield 75.0 %) were obtained.

(0516)

NMR (CDCl₃) delta: 1.12 (9H, s), 1.38 (9H, s), 6.87 (1H, dd, J = 8 Hz, 2 Hz), 7.07 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.22-7.29 (3H, m), 7.32-7.38 (3H, m), 7.67 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.75 (1H, d, J = 8 Hz), 7.99 (1H, dd, J = 8 Hz, 2 Hz), 8.15 (1H, br-s), 8.50 (1H, dd, J = 8 Hz, 2 Hz) 9.519 (1H, s), 10,17 (1H, s).

IR (ν, cm⁻¹, KBr): 2224, 1714, 1652, 1594, 1580, 1564, 1530, 1498.

EI-MS (m/z, %): 531 (m +, 85), 175 (100), 260 (53).

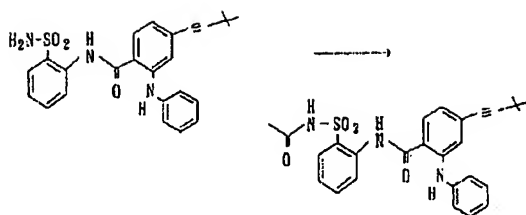
mp: 218-219 degrees.

(0517)

Example 81

N-(2-(4-(3,3-dimethyl butenyl)-2-phenylamino benzamide) benzenesulphonyl) acetamide.

(0518)



(0519)

Acetic anhydride 0.07 ml (0.74 mmol) was added under a stream of nitrogen to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 180 mg (1.47 mmol) and 4-(3,3-dimethyl butenyl)-2-phenylamino-N-(2-sulphamoyl phenyl) benzamide 300 mg (0.67 mmol) produced in Example 70, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 235 mg (yield 72.0 %) were obtained.

(0520)

NMR (CDCl₃) delta: 1.28 (9H, s), 2.04 (3H, s), 6.85 (1H, dd, J = 8 Hz, 2 Hz), 7.07 (1H, dd, J = 8 Hz, 8 Hz), 7.22-7.29 (3H, m), 7.31-7.39 (3H, m), 7.66 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.73 (1H, d, J = 8 Hz), 7.99 (1H, dd, J = 8 Hz, 2 Hz), 8.26 (1H, br-s), 8.55 (1H, dd, J = 8 Hz, 2 Hz) 9.49 (1H, s), 10.24 (1H, s).

IR (ν, cm⁻¹, KBr): 2224, 1730, 1658, 1582, 1556, 1538, 1498, 1470, 1442, 1418, 1336, 1270.

EI-MS (m/z, %): 489 (m +, 73), 275 (100), 260 (70).

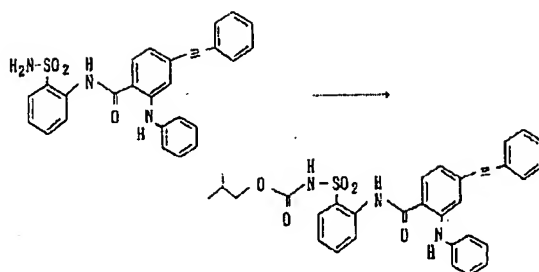
mp: 208-209 degrees.

(0521)

Example 82

N-(2-((2-methylpropyl oxycarbonyl amino) sulphonyl) phenyl) 2-phenylamino-4-phenyl-ethynyl benzamide.

(0522)



(0523)

Chlorocarbonic acid isobutyl ester 0.15 ml (1.18 mmol) was added under a stream of nitrogen to tetrahydrofuran (10 ml) solution of 4-dimethylaminopyridine 289 mg (2.36 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 500 mg (1.07 mmol) produced in Example 73, and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 455 mg (yield 75.0 %) were obtained.

(0524)

NMR (delta, CDCl₃): 0.83 (6H, d, J = 7 Hz), 1.80-1.90 (1H, m), 3.85 (2H, d, J = 7 Hz), 6.98 (1H, dd, J = 8 Hz, 2 Hz), 7.10 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.24-7.31 (4H, m), 7.32-7.39 (4H, m), 7.47-7.55 (3H, m), 7.60 (1H, br-s), 7.68 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.76 (1H, d, J = 8 Hz), 8.03 (1H, dd, J = 8 Hz, 2 Hz), 8.61 (1H, dd, J = 8 Hz, 2 Hz), 9.57 (1H, s), 10.27 (1H, s).

IR (v, cm⁻¹, KBr): 2212, 1716, 1674, 1582, 1556, 1516, 1472, 1424, 1356, 1226.

FAB-MS (m/z, %): 566 (M-H, 23), 265 (100).

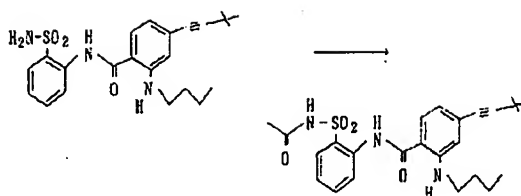
mp: 155-156 degrees.

(0525)

Example 83

N-(2-(2-butylamino-4-(3,3-dimethyl butenyl) benzamide) benzensulphonyl) acetamide.

(0526)



(0527)

Acetic anhydride 0.07 ml (0.74 mmol) were added under a stream of nitrogen to tetrahydrofuran (10 ml) solution of 2-butylamino-4-(3,3-dimethyl butenyl)-N-(2-sulphamoyl phenyl) benzamide 300 mg (0.70 mmol) and 4-dimethylaminopyridine 189 mg (1.55 mmol), and it was stirred at room temperature for one hour, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 250 mg (yield 76.0 %) were obtained.

(0528)

NMR (delta, CDCl₃): 0.96 (3H, t, J = 7 Hz), 1.33 (9H, s), 1.44-1.56 (2H, m), 1.63-1.70 (2H, m), 2.04 (3H, s), 3.18 (2H, t, J = 7 Hz), 6.66 (1H, dd, J = 8 Hz, 2 Hz), 6.72 (1H, d, J = 2 Hz), 7.24 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.61 (1H, d, J = 8 Hz), 7.65 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.81 (1H, br-s), 8.01 (1H, dd, J = 8 Hz, 2 Hz), 8.20 (1H, br-s), 8.48 (1H, dd, J = 8 Hz, 1 Hz), 10.02 (1H, s).

IR (ν, cm⁻¹, KBr): 3392, 3196, 2972, 2932, 2872, 2228, 1736, 1640, 1598, 1584, 1564, 1530, 1474, 1444, 1348, 1290, 1236, 1212, 1154, 854, 766.

EI-MS (m/z, %): 489 (m +, 73), 275 (100), 260 (70).

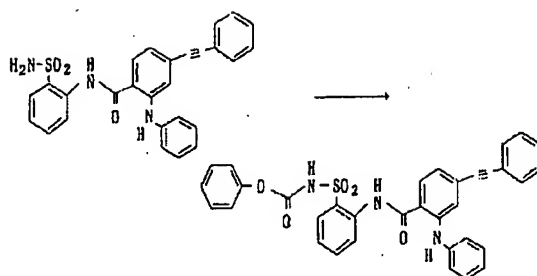
mp: 155-156 degrees.

(0529)

Example 84

2-phenylamino-4-phenyl-ethynyl-N-(2-(phenyloxy carbonylamino) sulphonyl) phenyl) benzamide.

(0530)



(0531)

Chlorocarbonic acid phenyl 0.18 ml (1.42 mmol) was added under a stream of nitrogen to ethyl acetate (10 ml) solution of 4-dimethylaminopyridine 316 mg (2.60 mmol) and 2-phenylamino-4-phenyl-ethynyl-N-(2-sulphamoyl phenyl) benzamide 548 mg (1.18 mmol) produced in Example 73, and it was stirred at room temperature for one hour. The reaction solution was washed successively with aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was washed with ether, and title compound 520 mg (yield 75.0 %) were obtained.

(0532)

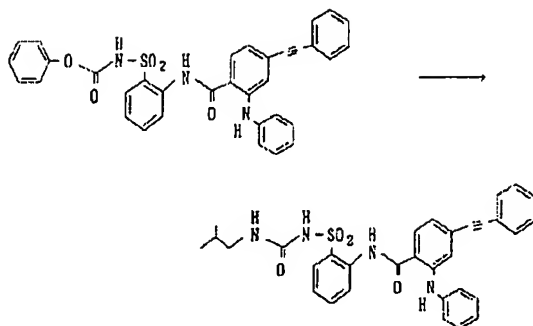
NMR (CDCl₃) delta: 6.96 (1H, dd, J = 8 Hz, 2 Hz), 7.00-7.04 (2H, m), 7.11 (1H, dd, J = 8 Hz, 8 Hz), 7.18-7.38, (11H, m), 7.45 (1H, d, J = 2 Hz), 7.49-7.53 (2H, m), 7.68-7.74 (2H, m), 7.82 (1H, br-s), 8.09 (1H, dd, J = 8 Hz, 2 Hz), 8.63 (1H, dd, J = 8 Hz, 1 Hz), 9.50 (1H, s), 10.23 (1H, s).
IR (ν, cm⁻¹, KBr): 3392, 3064, 2864, 2216, 1748, 1646, 1582, 1560, 1528, 1498, 1476, 1442, 1420, 1360, 1320, 1288, 1226, 1198, 1162, 1128, 898, 754.
FAB-MS (m/z, %): 586 (M-H, 22), 451 (100).
mp: 146-147 degrees.

(0533)

Example 85

2-phenylamino-4-phenyl-ethynyl-N-(2-((2-methylpropyl amino) carbonylamino) sulfonyl) phenyl) benzamide.

(0534)



(0535)

2-phenylamino-4-phenyl-ethynyl-N-(2-((phenyloxy carbonylamino) sulfonyl) phenyl) benzamide 105 mg (0.18 mmol) produced in Example 84 and benzene (5 ml) solution of isobutyl amine 0.04 ml (0.36 mmol) were heated under reflux for two hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with acetonitrile, and title compound 70 mg (yield 69.0 %) were obtained.

(0536)

NMR (CDCl₃) delta: 0.83 (6H, d, J = 7 Hz), 1.64-1.71 (1H, m), 2.91 (2H, dd, J = 7 Hz, 6 Hz), 6.23 (1H, br-s), 6.94 (1H, dd, J = 8 Hz, 2 Hz), 7.10 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.21-7.28 (3H, m), 7.32-7.40 (5H, m), 7.45 (1H, d, J = 2 Hz), 7.48-7.53 (2H, m), 7.66 (1H, ddd, J = 8 Hz, 8 Hz, 2 Hz), 7.69 (1H, d, J = 8 Hz), 7.88 (1H, dd, J = 8 Hz, 2 Hz), 8.36 (1H, br-s), 8.56 (1H, dd, J = 8 Hz, 1 Hz), 9.56 (1H, s), 10.00 (1H, s).

IR (ν, cm⁻¹, KBr): 3392, 3268, 3064, 2960, 2932, 2220, 1682, 1658, 1580, 1554, 1530, 1498, 1472, 1442, 1418, 1344, 1320, 1288, 1224, 1152, 752.

FAB-MS (m/z, %): 565 (M-H, 16), 265 (100).

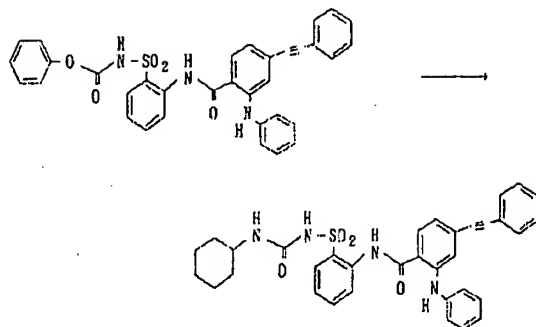
mp: 183-184 degrees.

(0537)

Example 86

N-(2-((cyclohexyl amino) carbonylamino) sulfonyl) phenyl) 2-phenylamino-4-phenyl-ethynyl benzamide.

(0538)



(0539)

2-phenylamino-4-phenyl-ethynyl-N-(2-(phenyloxy carbonylamino) sulphonyl) phenyl benzamide 200 mg (0.34 mmol) produced in Example 84 and benzene (5 ml) solution of cyclohexylamine 0.09 ml (0.75 mmol) were heated under reflux for two hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with acetonitrile, and title compound 136 mg (yield 67.0 %) were obtained.

(0540)

NMR (delta, CDCl₃): 1.06 (2H, m), 1.20-1.28 (2H, m), 1.45-1.70 (4H, m), 1.75-1.85 (2H, m), 3.45-3.55 (1H, m), 6.00 (1H, br-s), 6.96 (1H, dd, J = 8 Hz, 2 Hz), 7.11 (1H, ddd, J = 8 Hz, 8 Hz, 1 Hz), 7.24-7.30 (5H, m), 7.32-7.40 (4H, m), 7.46 (1H, d, J = 2 Hz), 7.49-7.53 (2H, m), 7.64-7.74 (3H, m), 7.89 (1H dd, J = 8 Hz, 2 Hz), 8.57 (1H, dd, J = 8 Hz, 1 Hz), 9.55 (1H, s), 10.03 (1H, s).

IR (ν, cm⁻¹, KBr): 3400, 3316, 3240, 2940, 2856, 2212, 1686, 1662, 1584, 1556, 1530, 1498, 1470, 1444, 1422, 1338, 1284, 1252, 1218, 1154, 1128, 1028, 756.

FAB-MS (m/z, %): 591 (M-H, 9), 311 (100).

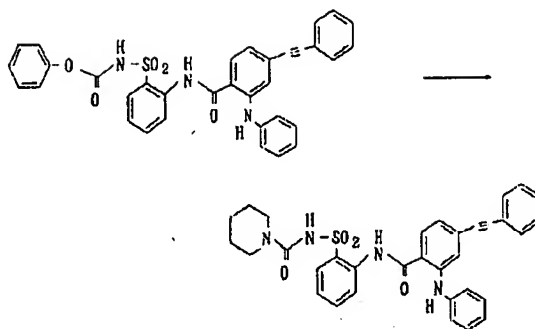
mp: 188-189 degrees.

(0541)

Example 87

2-phenylamino-4-phenyl-ethynyl-N-(2-(piperidino carbonylamino) sulfonyl) phenyl benzamide.

(0542)



(0543)

2-phenylamino-4-phenyl-ethynyl-N-(2-((phenyloxy carbonylamino) sulfonyl) phenyl) benzamide 200 mg (0.34 mmol) produced in Example 84 and benzene (5 ml) solution of piperidine 0.07 ml (0.75 mmol) were heated under reflux for two hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with acetonitrile, and title compound 94 mg (yield 50.0 %) were obtained.

(0544)

NMR (δ , CDCl_3): 1.55 (6H, br-s), 3.32 (4H, br-s), 6.98 (1H, dd, $J = 8$ Hz, 2 Hz), 7.08 (1H, ddd, $J = 8$ Hz, 8 Hz, 1 Hz), 7.24-7.30 (5H, m), 7.31-7.39 (4H, m), 7.47-7.57 (3H, m), 7.64 (1H, ddd, $J = 8$ Hz, 8 Hz, 2 Hz), 7.90 (1H, d, $J = 8$ Hz), 8.00 (1H, dd, $J = 8$ Hz, 2 Hz), 8.49 (1H, dd, $J = 8$ Hz, 1 Hz), 9.64 (1H, s), 10.53 (1H, s).

IR (ν , cm^{-1} , KBr): 3268, 2940, 2860, 2212, 1682, 1660, 1582, 1562, 1536, 1498, 1478, 1442, 1422, 1316, 1286, 1256, 1228, 1160, 752.

FAB-MS (m/z , %): 577 (M-H, 100), 265 (66).

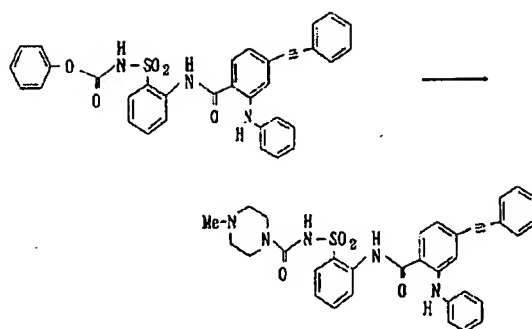
mp: 163-164 degrees.

(0545)

Example 88

N-(2-((4-methyl piperazinyl) carbonylamino) sulfonyl) phenyl) 2-phenylamino-4-phenyl-ethynyl benzamide.

(0546)



(0547)

2-phenylamino-4-phenyl-ethynyl-N-(2-(phenyloxy carbonylamino) sulphonyl) phenyl) benzamide 160 mg (0.27 mmol) produced in Example 84 and benzene (5 ml) solution of 1-methylpiperazine 0.07 ml (0.75 mmol) were heated under reflux for two hours. Water was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water, aqueous potassium hydrogen sulphate solution and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised with acetonitrile, and title compound 130 mg (yield 81.0 %) were obtained.

(0548)

NMR (delta, CDCl₃): 2.23 (4H, br-s), 3.44 (4H, br-s), 6.84 (1H, d, J = 8 Hz), 6.94-7.04 (2H, m), 7.16 (2H, d, J = 8 Hz), 7.21-7.30 (6H, m), 7.34-7.44 (4H, m), 7.76 (1H, d, J = 8 Hz), 7.93 (1H, br-s), 8.33 (1H, d, J = 8 Hz), 9.56 (1H, s), 10.39 (1H, s).

IR (ν, cm⁻¹, KBr): 3316, 3056, 2940, 2856, 2800, 2212, 1660, 1590, 1556, 1536, 1498, 1464, 1442, 1420, 1320, 1292, 1266, 1226, 1142, 1106, 756.

FAB-MS (m/z, %): 592 (M-H, 62), 197 (100).

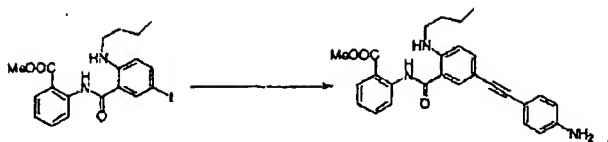
mp: 181-182 degrees.

(0549)

Reference Example 44

2-((4-amino) phenyl-ethynyl-2-butylamino benzamide) methyl benzoate ester.

(0550)



(0551)

4-ethynyl aniline 200 mg (1.72 mmol), dichlorobis triphenylphosphine palladium 23 mg (0.03 mmol) and copper iodide 12 mg (0.06 mmol) were added to mixed solution of diethylamine (12 ml) of 2-(2-butylamino-5-iodobenzamide) methyl benzoate 300 mg (0.66 mmol) and tetrahydrofuran (5 ml), and the mixture was stirred at room temperature for 20 hours, and next the solvent was eliminated by distillation under reduced pressure. Water was added to the residue, and thereafter, extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 270 mg (yield 92.6 %) were obtained.

(0552)

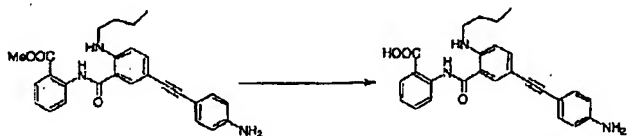
NMR (delta, CDCl₃): 0.97 (3H, t, J = 7 Hz), 1.42-1.52 (2H, m), 1.64-1.72 (2H, m), 3.18-3.22 (2H, m), 3.78 (2H, s), 3.97 (3H, s), 6.63 (2H, d, J = 8 Hz), 6.68 (1H, d, J = 9 Hz), 7.08-7.14 (1H, m), 7.33 (2H, d, J = 8 Hz), 7.46 (1H, dd, J = 9.2 Hz), 7.55-7.61 (1H, m), 7.88 (1H, d, J = 2 Hz), 7.95 (1H, t, J = 5 Hz), 8.07 (1H, dd, J = 8.1 Hz), 8.66-8.72 (1H, d, J = 8 Hz), 11.71 (1H, s).

(0553)

Example 89

2-((4-amino) phenyl-ethynyl-2-butylamino benzamide) benzoic acid.

(0554)



(0555)

1M-sodium hydroxide solution 3 ml were added to dioxane (20 ml) solution of 2-((4-amino) phenyl-ethynyl-2-butylamino benzamide) methyl benzoate 270 mg (0.61 mmol) produced in Reference

Example 44, and the mixture was stirred at room temperature for 24 hours. 1M-hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 170 mg (yield 65.2 %) were obtained.

(0556)

NMR (delta, CDCl₃): 0.98 (3H, t, J = 7 Hz), 1.43-1.54 (2H, m), 1.64-1.74 (2H, m), 3.21 (2H, t, J = 7 Hz), 6.57 (2H, d, J = 8 Hz), 6.69 (1H, d, J = 9 Hz), 6.97-7.04 (1H, m), 7.33 (2H, d, J = 8 Hz), 7.47 (1H, dd, J = 9.2 Hz), 7.57-7.64 (1H, m), 7.88 (1H, d, J = 2 Hz), 8.01 (1H, dd, J = 8.1 Hz), 8.78 (1H, d, J = 8 Hz), 11.68 (1H, s).

IR (ν, cm⁻¹, KBr): 3396, 1652, 1592, 1528, 1224, 764.

FAB-MS (m/z, %): 426 (M-H, 100).

mp: 190 degradation.

(0557)

Reference Example 45

2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester.

(0558)



(0559)

Thionyl chloride 2.0 ml and several drops of N, N-dimethylformamide was added to anhydrous benzene (20 ml) solution of 2-chloro-5-phenylethynyl benzoic acid 2.8 g (10.91 mmol) and were heated under reflux for one hour, and thereafter, the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and this was dropwise-added under ice cooling to mixed solution of potassium carbonate 2.3 g (16.36 mmol), water (20 ml) of 2-ethyl aminobenzoic acid 1.6 ml (10.91 mmol) and ethyl acetate (10), and it was stirred at room temperature for 18 hours. The organic layer was separated, and the aqueous layer was extracted with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was

eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 4.12 g (yield 93.5 %) were obtained.

(0560)

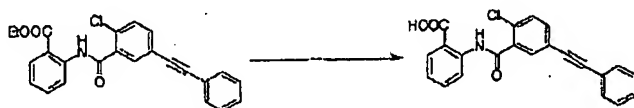
NMR (delta, CDCl₃): 1.40 (3H, t, J = 7 Hz), 4.37 (2H, q, J = 7 Hz), 7.14-7.20 (1H, m) 7.34-7.40 (3H, m), 7.45 (1H, d, J = 8 Hz), 7.50-7.58 (3H, m), 7.60-7.66 (1H, m), 7.80 (1H, d, J = 2 Hz), 8.10 (1H, dd, J = 8.1 Hz), 8.88 (1H, d, J = 8 Hz), 11.57 (1H, s).

(0561)

Reference Example 46

2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid.

(0562)



(0563)

1M-sodium hydroxide solution 30 ml were added to ethanol (20 ml) solution of 2-(2-chloro-5-phenyl-ethynyl benzamide) benzoic acid ethyl ester 4.12 g (10.20 mmol) produced in Reference Example 45, and the mixture was heated under reflux for three hours. 1M-concentrated hydrochloric acid was added to the reaction solution, and it was acidified, and next extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was recrystallised using ethyl acetate-hexane, and title compound 3.26 g (yield 85.0 %) were obtained.

(0564)

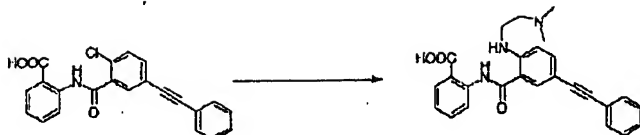
NMR (delta, CDCl₃): 7.14-7.20 (1H, m), 7.33-7.38 (1H, d, J = 8 Hz), 7.50-7.58 (3H, m), 7.64-7.70 (1H, m), 7.81 (1H, d, J = 2 Hz), 8.12 (1H, dd, J = 8.1 Hz), 8.98 (1H, d, J = 8 Hz), 11.39 (1H, s).

(0565)

Example 90

2-((2-dimethylamino) ethylamino-5-phenyl-ethynyl benzamide) benzoic acid.

(0566)



(0567)

Potassium carbonate 0.40 g (2.87 mmol) and 5 wt.% activated copper was added to N, N-dimethylethylenediamine (8 ml) solution of 2-(2-chloro-5-phenylethynyl benzamide) benzoic acid ethyl ester 0.90 g (2.39 mmol) produced in Reference Example 46, and it was heated with stirring at 180 degrees in sealed tube for three hours and next it was cooled to room temperature. 1M-hydrochloric acid was added to the reaction solution, and extraction was carried out with acetic acid ethyl ester. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and it was dried with anhydrous sodium sulphate, and next the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel chromatography, and title compound 0.42 g (yield 41.1 %) were obtained.

(0568)

NMR (delta, DMSO-d₆): 2.83 (6H, s), 3.29 (2H, t, J = 7 Hz), 3.64-3.74 (2H, m), 6.98 (1H, d, J = 9 Hz), 7.19-7.26 (1H, m), 7.40-7.46 (3H, m), 7.49-7.55 (2H, m), 7.58 (1H, dd, J = 9.2 Hz), 7.62-7.68 (1H, m), 7.91 (1H, d, J = 2 Hz), 7.94-8.00 (1H, m), 8.04 (1H, dd, J = 8.1 Hz), 8.53 (1H, d, J = 8 Hz), 11.98 (1H, s).

IR (ν, cm⁻¹, KBr): 2208, 1680, 1660, 1592, 1530, 1228, 754

FAB-MS (m/z, %): 426 (M-H, 100).

mp: 181-183 degrees.

(0569)

Pharmacological Test 1

Measurement of ACC inhibiting activity

1. Purification of ACC.

12 week old male SD series rats were fasted for two days, and thereafter, high sucrose food (67 % sucrose, 17.1 % casein, 9.8 % cellulose, 5 % salt, 0.1 % choline chloride, 1 % vitamins) was given for two days, and decapitation under ether anaesthesia and bleeding were carried out, next liver was quickly removed. This liver was diced in ice cooled buffer A (225 mM mannitol, 75 mM sucrose, 10 mM Tris / HCl [pH 7.5], 0.05 mM EDTA-2Na, 5 mM potassium citrate, 2.5 mM MnCl₂, 10 mg/l

aprotinin, 10 mg/l leupeptin, 10 mg/l antitrypsin), and water content was eliminated, thereafter buffer A was added so as to become 5 ml/g, and it was homogenised with Polytron homogenizer for four minutes. This was centrifuged and separated at 1,000 g for ten minutes and next supernatant was centrifuged at high speed at 17,000 g for ten minutes and was separated.

(0570)

Ammonium sulphate was added so as to form 35 %, and the obtained supernatant was stirred for 45 minutes and it was centrifuged at high speed at 17,000 g for ten minutes and was separated. Buffer B of 100 ml (100 mM Tris / HCl [pH 7.5], 0.5 M NaCl, 1 mM EDTA-2Na, 0.1 mM DTT, 10 % glycerol, 10 mg/l aprotinin, 10 mg/l leupeptin, 10 mg/l antitrypsin) was added to the obtained precipitation, and it was ultracentrifuged and separated at 40,000 g for 20 minutes, supernatant was dialysed overnight with buffer C of 150 fold volume (100 mM Tris / HCl [pH 7.5], 0.5M NaCl, 1 mM EDTA-2Na, 0.1 mM DTT, 10 % glycerol), and filtration was carried out with filter of 5 µm. Filtrate was applied to biotin affinity column and was washed with buffer B, and thereafter, ACC was eluted with buffer B which included 5 mM biotin.

(0571)

2. Measurement of ACC inhibiting activity

Compounds produced in aforesaid Examples were each dissolved in DMSO, and introduced into glass vials, and reagent 1 containing 250 µl ACC (40 mM Tris / HCl [pH 7.5], 40 mM MgCl₂, 40 mM sodium citrate, 2 mM DTT, 100 µg/ml fatty acid free BSA) was added, and it was warmed in a thermostat bath at 37 degrees for 30 minutes. After ice cooling, reagent 2 of 250 µl (40 mM Tris / HCl [pH 7.5], 2 mM DTT, 8 mM ATP, 0.5 mM acetyl CoA) containing NaH[¹⁴C]CO₃ of 74 kBq was added, and further it was warmed in a thermostat bath at 37 degrees for ten minutes, and next 1N-HCl of 0.1 ml was added, and reaction was stopped. Water content in glass vial was completely eliminated under reduced pressure, and emulsification scintillator (Cleansol I) was added to the glass vial, and radioactivity of ¹⁴C was measured using liquid scintillation counter. Inhibition activity of each compound (5.6×10^{-6} mol) was determined. The results thereof are shown in Table 1.

(0572)

Pharmacological Test 2

Measurement of inhibiting activity (FA biosynthesis inhibiting activity) with respect to fatty acid synthesis in cell

Compounds produced in aforesaid Examples were each dissolved using DMSO and was added to experiment culture medium (DMEM, 0.05 µg/ml Insulin, 0.1 mg/ml glucose, 18.5 kBq/ml (¹⁴C)-

glucose). It was prepared to form 0.75×10^6 cells/ml. Moreover, HepG2 cells were inoculated by 1 ml/well in 12-well plate, and it was cultured overnight (culture solution: DMEM, 4.5 g/ml, glucose, 10 % FBS), at 5 % CO₂, 37 deg C, thereafter the cells were washed twice with PBS (-) buffer, and next experiment culture medium was added by 0.5 ml/well, and it was cultured at 5 % CO₂, 37 deg C for three hours. After culturing, the cells were washed twice with ice cooled PBS (-) buffer, and lipid of the cells which were scraped off was extracted with lipid extraction liquid (chloroform : methanol = 2:1). Ethanol 2.5 ml and 33 % potassium hydroxide 0.1 ml were added to the extract, and it was placed on a water bath at 70 degrees for one hour. Lipid was extracted from this reactant again, and extract was applied to silica gel thin layer plate. This was developed using developing solution (hexane : diethyl ether : acetic acid = 80:20:1), and thereafter, iodine colouring site of fatty acid was collected, and radioactivity thereof was measured using liquid scintillation counter. Inhibiting activity % of each compound (3.0×10^{-5} M) was determined. The results thereof are shown in Table 1.

(0573)

(Table 1)

| Ex. No. | Compound name | ACC inhibition activity (%) (5.6×10^{-6} M) | FA synthesis inhibition (%) (3.0×10^{-5} M) |
|---------|---|--|--|
| 7 | 2-(4-benzyloxy-2-phenylaminobenzamide) benzoic acid | 22.8 | 92.3 |
| 8 | 2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid | 53.7 | 76.2 |
| 9 | 2-[4-phenylethynyl-2-(3-trifluoromethylphenylamino) benzamide] benzoic acid | 61.3 | 66.5 |
| 15 | 2-(2-hexylamino-4-phenylethynylbenzamide) benzoic acid | 40.2 | 66.5 |
| 16 | 2-(2-benzylamino-4-phenylethynylbenzamide) benzoic acid | 57.8 | 51.2 |
| 21 | 2-(2-n-octylaminobenzamide) benzoic acid | 41.5 | 37.2 |
| 22 | 2-(2-n-decylaminobenzamide) benzoic acid | 37.3 | 36.0 |
| 30 | 2-(2,6-dihexylaminobenzamide) benzoic acid | 38.4 | 91.6 |
| 31 | 2-[4-phenylethynyl-2-(3-phenylpropylamino) benzamide] benzoic acid | 93.7 | 50.5 |
| 33 | 2-(2-butylamino-4-phenylethynylbenzamide) benzoic acid | 69.0 | 54.9 |
| 35 | 2-[5-phenylethynyl-2-(3-phenylpropyl) aminobenzamide] benzoic acid | 69.0 | 54.9 |
| 36 | 2-(2-phenylamino-5-phenylethynylbenzamide) benzoic acid | 87.8 | 82.8 |
| 37 | 2-(2-methylamino-4-phenylethynylbenzamide) benzoic acid | 41.7 | 78.6 |

(0574)

(Table 2)

| Ex. No. | Compound name | ACC inhibition activity (%) (5.6×10^{-6} M) | FA synthesis inhibition (%) (3.0×10^{-5} M) |
|---------|--|--|--|
| 40 | 2-[2-butylamino-5-(4-nitrophenyl) ethynylbenzamide] benzoic acid | 69.9 | 80.5 |
| 41 | 2-[2-butylamino-5-(4-cyanophenyl) ethynylbenzamide] benzoic acid | 80.5 | 85.3 |
| 42 | 2-[2-butylamino-5-(4-hydroxyphenyl) ethynylbenzamide] benzoic acid | 92.5 | 54.7 |
| 43 | 2-(2-methylamino-5-phenylethynylbenzamide) benzoic acid | 79.0 | 97.3 |
| 44 | 2-(2-ethylamino-5-phenylethynylbenzamide) benzoic acid | 86.5 | 98.3 |
| 45 | 2-(2-propylamino-5-phenylethynylbenzamide) benzoic acid | 87.6 | 95.0 |
| 46 | 2-(2-butylamino-5-phenylethynylbenzamide) benzoic acid | 79.8 | 85.7 |
| 47 | 5-chloro-2-(4-benzyloxy-2-phenylaminobenzamide) benzoic acid | 73.1 | 77.6 |
| 49 | 3-(4-benzyloxy-2-phenylaminobenzamide)-2-naphthalene carboxylic acid | 75.2 | 56.6 |
| 52 | 2-(4-benzyloxy-2-phenylaminobenzamide)-5-hydroxy benzoic acid | 49.4 | 25.5 |
| 53 | 5-chloro-2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid | 84.1 | 64.4 |
| 55 | 3-(2-phenylamino-4-phenylethynylbenzamide)-2-naphthalene carboxylic acid | 58.9 | 42.4 |

(0575)

(Table 3).

| Ex. No. | Compound name | ACC inhibition activity (%) (5.6×10^{-6} M) | FA synthesis inhibition (%) (3.0×10^{-5} M) |
|---------|---|--|--|
| 55 | 5-methoxy-2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid | 76.3 | 53.6 |
| 57 | 5-methyl-2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid | 78.0 | 67.6 |
| 59 | 3-(2-phenylamino-4-phenylethynylbenzamide) thiophene benzoic acid | 55.1 | 85.3 |
| 60 | 5-bromo-2-(2-phenylamino-4-phenylethynylbenzamide) benzoic acid | 82.2 | 67.1 |
| 61 | 1-(2-phenylamino-4-phenylethynylbenzamide) cyclohexane carboxylic acid | 30.0 | 70.3 |
| 62 | 2-[4-(octan-1-yl)-2-phenylaminophenylamino benzamide] benzoic acid | 67.4 | 70.2 |
| 63 | 2-[4-(3,3-dimethylbutynyl)-2-phenylamino benzamide] benzoic acid | 80.7 | 87.0 |
| 64 | 2-[2-phenylamino-4-(bentan-1-yl) benzamide benzoic acid | 74.1 | 87.2 |
| 65 | 2-[2-butylamino-4-(3,3-dimethylbutynyl) benzamide] benzoic acid | 48.5 | 59.6 |
| 66 | 2-[2-butylamino-5-(2-pyridylethynyl) benzamide] benzoic acid | 47.8 | 72.2 |
| 67 | 2-[2-butylamino-5-(2-thiophenylethynyl) benzamide] benzoic acid | 56.7 | 65.6 |
| 74 | N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] benzamide | 52.9 | 58.6 |

(0576)

(Table 4).

| Ex. No. | Compound name | ACC inhibition activity (%) (5.6×10^{-6} M) | FA synthesis inhibition (%) (3.0×10^{-5} M) |
|---------|---|--|--|
| 75 | N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl]-4-trifluoromethylbenzamide | 26.0 | 14.6 |
| 76 | N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] acetamide | 87.5 | 69.4 |
| 77 | N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] hexanamide | 88.1 | 84.9 |
| 78 | N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] decanamide | 59.5 | 19.7 |
| 79 | N-[2-(2-phenylamino-4-phenylethynylbenzamide) benzenesulphonyl] pivalamide | 83.7 | 64.9 |
| 80 | N-[2-[4-(3,3-dimethylbutynyl)-phenylaminobenzamide] benzenesulphonyl] pivalamide | 87.5 | 69.4 |
| 81 | N-[2-[4-(3,3-dimethylbutynyl)-phenylaminobenzamide] benzenesulphonyl] acetamide | 28.0 | 84.4 |
| 82 | N-[2-[(2-methylproyloxycarbonylamino) sulphonyl] phenyl] 2-phenylamino-4-phenylethynylbenzamide | 91.9 | 67.2 |

(0577)

Advantages Afforded by this Invention

As described above, this invention puts forward novel aromatic amide derivatives represented by the above-mentioned general formula (I) as effective ACC activity inhibiting agent in therapy of visceral fat syndrome which is a risk factor of geriatric diseases such as cardiac infarction, cerebral infarction, diabetes mellitus or the like, and effect on medical care thereof is great.

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